

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
27 September 2001 (27.09.2001)

PCT

(10) International Publication Number  
WO 01/70727 A1(51) International Patent Classification<sup>7</sup>: C07D 401/04,  
401/14, A61K 31/506, A61P 25/28, C07D 405/14, 409/14

(21) International Application Number: PCT/EP01/03638

(22) International Filing Date: 22 March 2001 (22.03.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

|            |                            |    |
|------------|----------------------------|----|
| 00400804.1 | 23 March 2000 (23.03.2000) | EP |
| 00400805.8 | 23 March 2000 (23.03.2000) | EP |
| 00400806.6 | 23 March 2000 (23.03.2000) | EP |
| 2000-81938 | 23 March 2000 (23.03.2000) | JP |

(71) Applicants (for all designated States except US):  
SANOFI-SYNTHELABO [FR/FR]; 174, avenue de  
France, F-75013 Paris (FR). MITSUBISHI-TOKYO  
PHARMACEUTICALS, INC. [JP/JP]; 2-6, Nihon-  
bashi-Honcho 2-chome, Chuo-ku, Tokyo 103-8405 (JP).

(72) Inventors; and

(75) Inventors/Applicants (for US only): ALMARIO GAR-  
CIA, Antonio [ES/FR]; 26, avenue Roger Salengro,  
F-92290 Chatenay Malabry (FR). ANDO, Ryoichi  
[JP/JP]; c/o Mitsubishi-Tokyo Pharmaceuticals, Inc.,  
Yokohama Research Center, 1000, Kamoshida-cho,  
Aoba-Ku, Yokohama-shi, Kanagawa 227-0033 (JP).  
ARITOMO, Keiichi [JP/JP]; c/o Mitsubishi-Tokyo  
Pharmaceuticals, Inc., Yokohama Research Center, 1000,  
Kamoshida-cho, Aoba-Ku, Yokohama-shi, Kanagawa

227-0033 (JP). FROST, Jonathan, Reid [GB/FR]; 12,  
rue du Parc, F-91320 Wissous (FR). LI, Adrien, Tak  
[FR/FR]; 14, rue Pierre Bonnard, F-92260 Fontenay aux  
Roses (FR). SHODA, Aya [JP/JP]; c/o Mitsubishi-Tokyo  
Pharmaceuticals, Inc., Yokohama Research Center, 1000,  
Kamoshida-cho, Aoba-Ku, Yokohama-shi, Kanagawa  
227-0033 (JP). UEHARA, Fumiaki [JP/JP]; c/o Mit-  
subishi-Tokyo Pharmaceuticals, Inc., Yokohama Research  
Center, 1000, Kamoshida-cho, Aoba-Ku, Yokohama-shi,  
Kanagawa 227-0033 (JP). WATANABE, Kazutoshi  
[JP/JP]; c/o Mitsubishi-Tokyo Pharmaceuticals, Inc.,  
Yokohama Research Center, 1000, Kamoshida-cho,  
Aoba-Ku, Yokohama-shi, Kanagawa 227-0033 (JP).

(74) Agent: KUGEL, Dominique; Sanofi-Synthelabo, 174,  
avenue de France, F-75013 Paris (FR).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM,  
HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,  
LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX,  
MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL,  
TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

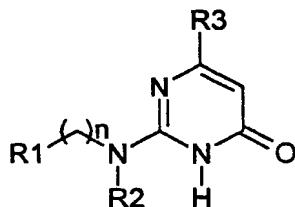
(84) Designated States (regional): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian  
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European  
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,  
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,  
CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

[Continued on next page]

(54) Title: 2-(ARYLALKYLAMINO)PYRIMIDONE DERIVATIVES AND 2-(HETEROARYLALKYLAMINO)PYRIMIDONE  
DERIVATIVES



(I)

(57) Abstract: A pyrimidine derivative represented by formula (I) or a salt thereof, wherein R2 represents a hydrogen atom, a C<sub>1-2</sub> perhalogenated alkyl group or a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 groups selected from a halogen atom, an amino, a (C<sub>1-6</sub>-alkyl)carbonylamino group, a (C<sub>1-6</sub>-alkoxy)carbonylamino group, a C<sub>1-6</sub> alkylsulfonylamino group or a phenyl group; R3 represents a 2, 3 or 4-pyridyl group optionally substituted by a C<sub>1-4</sub> alkyl group, C<sub>1-4</sub> alkoxy group or a halogen atom; and when n represents 1 to 10, the R1 represents an unsubstituted naphth-1-yl group; an unsubstituted naphth-2-yl group; a C<sub>6,10</sub> aryl group substituted by 1 to 3 substituents (A); a furan ring, thiophene ring, pyrrole ring or imidazole ring, the rings being optionally substituted by 1 to 3 substituents (A); an indole ring, attached by a carbon atom, optionally substituted by 1 to 3 substituents (A), the nitrogen of the indole ring being optionally substituted by a C<sub>1-6</sub> alkyl group; a pyridine ring optionally substituted by 1 to 3 substituents (B); when n represents 4 to 10 then R1 can represent in addition an unsubstituted phenyl group; and when n represents 1 to 3 and R1 represents an unsubstituted phenyl group then R2 represents a C<sub>1-2</sub> perhalogenated alkyl group or a C<sub>1-6</sub> alkyl substituted by 1 to 3 groups selected from a halogen atom, an amino, a (C<sub>1-6</sub>-alkyl)carbonylamino group, a (C<sub>1-6</sub>-alkoxy)carbonylamino group, a C<sub>1-6</sub> alkylsulfonylamino group. And a medicament comprising the said derivative or a salt thereof as an active ingredient which is used for preventive and/or therapeutic treatment of a neurodegenerative disease caused by abnormal activity of GSK3β.

WO 01/70727 A1



— before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

## SPECIFICATION

2-(ARYLALKYLAMINO)PYRIMIDONE DERIVATIVES AND  
2-(HETEROARYLALKYLAMINO)PYRIMIDONE DERIVATIVES

5

## Technical Field

The present invention relates to compounds that are useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal activity of GSK3 $\beta$ .

10

## Background Art

GSK3 $\beta$  (glycogen synthase kinase 3 $\beta$ ) is a proline directed serine, threonine kinase that plays an important role in the control of metabolism, differentiation and survival. It was initially identified as an enzyme able to phosphorylate and hence inhibit glycogen synthase. It was later recognized that GSK3 $\beta$  was identical to tau protein kinase 1 (TPK1), an enzyme that phosphorylates tau protein in epitopes that are also found to be hyperphosphorylated in Alzheimer's disease and in several taupathies.

20

Interestingly, protein kinase B (AKT) phosphorylation of GSK3 $\beta$  results in a loss of its kinase activity, and it has been hypothesized that this inhibition may mediate some of the effects of neurotrophic factors. Moreover, phosphorylation by GSK3 $\beta$  of  $\beta$ -catenin, a protein involved in cell survival, results in its degradation by an ubiquitination dependent proteasome pathway.

25

Thus, it appears that inhibition of GSK3 $\beta$  activity may result in neurotrophic activity. Indeed there is evidence that lithium, an uncompetitive inhibitor of GSK3 $\beta$ , enhances neuritogenesis in some models and also increases neuronal survival, through the induction of survival factors such as Bcl-2 and the inhibition of the expression of proapoptotic factors such as P53 and Bax.

30

Recent studies have demonstrated that  $\beta$ -amyloid increases the GSK3 $\beta$  activity and tau protein phosphorylation. Moreover, this hyperphosphorylation as well as the neurotoxic effects of  $\beta$ -amyloid are blocked by lithium chloride and by a GSK3 $\beta$  antisense mRNA. These observations strongly suggest that GSK3 $\beta$  may be the link between the two major pathological processes in Alzheimer's disease : abnormal APP (Amyloid Precursor protein) processing and tau protein hyperphosphorylation.

35

Although tau hyperphosphorylation results in a destabilization of the neuronal

cytoskeleton, the pathological consequences of abnormal GSK3 $\beta$  activity are, most likely, not only due to a pathological phosphorylation of tau protein because, as mentioned above, an excessive activity of this kinase may affect survival through the modulation of the expression of apoptotic and antiapoptotic factors.

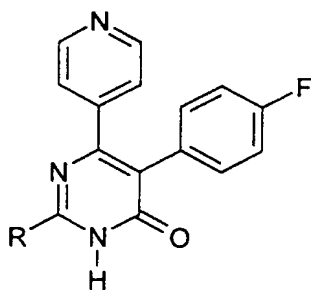
5 Moreover, it has been shown that  $\beta$ -amyloid-induced increase in GSK3 $\beta$  activity results in the phosphorylation and, hence the inhibition of pyruvate dehydrogenase, a pivotal enzyme in energy production and acetylcholine synthesis.

10 Altogether these experimental observations indicate that GSK3 $\beta$  may find application in the treatment of the neuropathological consequences and the cognitive and attention deficits associated with Alzheimer's disease, as well as other acute and chronic neurodegenerative diseases. These include, in a non-limiting manner, Parkinson's disease, tauopathies (e.g. frontotemporoparietal  
15 dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration); brain and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma.

20

In addition GSK3 $\beta$  may find application in the treatment of other diseases such as: Non-insulin dependent diabetes (such as diabetes type II ) and obesity; manic depressive illness; schizophrenia; alopecia; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-  
25 induced tumors.

PCT application WO 98/24782 discloses compounds represented by the following formula (A):



(A)

30

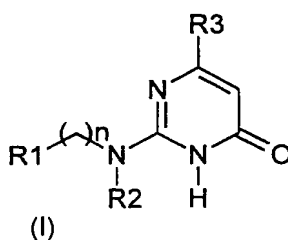
wherein R represents a 2,6-dichlorobenzyl group, a 2-(2-chlorophenyl)ethylamino group, a 3-phenylpropylamino group, or a 1-methyl-3-phenylpropylamino group. The compounds represented by formula (A) are characterized by a 4-fluorophenyl group at the 5-position of the pyrimidine ring. The main pharmacological activity disclosed for the compounds represented by formula (A) is an anti-inflammatory effect, whereas the compounds of the present invention represented by formula (I) herein below are useful as GSK3 $\beta$  inhibitors or as medicaments for the therapeutic treatment of neurodegenerative diseases, and therefore, their pharmacological activities are totally different.

## Disclosure of the Invention

An object of the present invention is to provide compounds useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of neurodegenerative diseases. More specifically, the object is to provide novel compounds useful as an active ingredient of a medicament that enables prevention and/or treatment of the neurodegenerative diseases such as Alzheimer's disease.

Thus, the inventors of the present invention have identified compounds possessing inhibitory activity against GSK3 $\beta$ . As a result, they found that compounds represented by the following formula (I) had the desired activity and were useful as an active ingredient of a medicament for preventive and/or therapeutic treatment of the aforementioned diseases.

The present invention thus provides pyrimidone derivatives represented by formula (I) or salts thereof, solvates thereof or hydrates thereof:



wherein:

R2 represents a hydrogen atom, a C<sub>1-2</sub> perhalogenated alkyl group or a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 groups selected from a halogen atom, an amino, a (C<sub>1-6</sub>-alkyl)carbonylamino group, a (C<sub>1-6</sub>-alkoxy)carbonylamino group, a C<sub>1-6</sub> alkylsulfonylamino group or a phenyl group;

R3 represents a 2, 3 or 4-pyridyl group optionally substituted by a C<sub>1-4</sub> alkyl group, C<sub>1-4</sub> alkoxy group or a halogen atom; and

- ◆ When n represents 1 to 10, then R1 represents
  - an unsubstituted naphth-1-yl group;
  - an unsubstituted naphth-2-yl group;
  - a C<sub>6,10</sub> aryl group substituted by 1 to 3 substituents (A);

- a furan ring, thiophene ring, pyrrole ring or imidazole ring, the rings being optionally substituted by 1 to 3 substituents (A);
  - an indole ring, attached by a carbon atom, optionally substituted by 1 to 3 substituents (A), the nitrogen of the indole ring being optionally substituted by a C<sub>1-6</sub> alkyl group;
- the substituent (A) being selected from a C<sub>1-6</sub> alkyl group, halogen atom, a C<sub>1-2</sub> perhalogenated alkyl group, a C<sub>1-3</sub> halogenated alkyl group, a hydroxyl group, a C<sub>1-6</sub> alkoxy group, methylenedioxy group, a nitro, a cyano, an amino, a C<sub>1-6</sub> monoalkylamino group, a C<sub>2-12</sub> dialkylamino group, a (C<sub>1-6</sub>-alkyl)carbonylamino group, a (C<sub>6,10</sub>-aryl)carbonylamino group, a (C<sub>1-6</sub>-alkoxy)carbonylamino group, aminocarbonyl group, a (C<sub>1-6</sub> monoalkylamino)carbonyl group, a (C<sub>2-12</sub> dialkylamino)carbonyl group, a formyl, a C<sub>1-6</sub> alkylcarbonyl group, a (C<sub>6,10</sub>-aryl)carbonyl group, a C<sub>1-5</sub> alkylsulfonyl group, a C<sub>6,10</sub> arylsulfonyl group, an aminosulfonyl group, a C<sub>1-6</sub> monoalkylaminosulfonyl group, a C<sub>2-12</sub> dialkylaminosulfonyl group, a phenyl group or a benzyloxy group;
- the C<sub>1-6</sub> alkyl groups and the C<sub>1-6</sub> alkoxy groups being optionally substituted by a halogen atom, a hydroxyl group, a C<sub>1-6</sub> alkoxy group, an amino, a C<sub>1-6</sub> monoalkylamino group, a C<sub>2-12</sub> dialkylamino group, a (C<sub>1-6</sub> alkyl)carbonylamino group, a (C<sub>6,10</sub> aryl)carbonylamino group, a (C<sub>1-6</sub> alkoxy)carbonylamino group, a C<sub>1-6</sub> alkylsulfonylamino group, a C<sub>6,10</sub> arylsulfonylamino group, a phenyl group, a pyridine, a pyrimidine, or a pyrimidin-2-yl-amino;
- a pyridine ring optionally substituted by 1 to 3 substituents (B);
- the substituent (B) being selected from a C<sub>1-18</sub> alkyl group, a C<sub>3-8</sub> cycloalkyl group, a C<sub>7-20</sub> aralkyl group, a C<sub>6-10</sub> aryl group, a fluorenyl group, a C<sub>1-6</sub> alkoxy group, a C<sub>3-8</sub> cycloalkyloxy group, a C<sub>7-20</sub> aralkyloxy group, a C<sub>6-14</sub> aryloxy group, a C<sub>1-5</sub> alkylthio group, a C<sub>7-20</sub> aralkylthio group, a C<sub>6-14</sub> arylthio group, a C<sub>1-5</sub> alkylsulfonyl group, a C<sub>6,10</sub> arylsulfonyl group, a halogen atom, a C<sub>1-2</sub> perhalogenated alkyl group, a C<sub>1-5</sub> halogenated alkyl group, a hydroxyl group, a cyano, a nitro, an oxo group, a formyl group, a C<sub>1-6</sub> alkylcarbonyl group, a (C<sub>6,10</sub>-aryl)carbonyl group, an amino, a C<sub>1-5</sub> monoalkylamino group, a C<sub>2-10</sub> dialkylamino group, or a heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5-10;

◆ When n represents 4 to 10 then R1 can represent in addition an unsubstituted

phenyl group; and

- ♦ When n represents 1 to 3 and R1 represents an unsubstituted phenyl group then R2 represents a C<sub>1-2</sub> perhalogenated alkyl group or a C<sub>1-6</sub> alkyl substituted by 1 to 3 groups selected from a halogen atom, an amino, a (C<sub>1-6</sub>-alkyl)carbonylamino group, a (C<sub>1-6</sub>-alkoxy)carbonylamino group and a C<sub>1-6</sub> alkylsulfonylamino group.

According to another aspect of the present invention, there is provided a medicament comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives represented by formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof. As preferred embodiments of the medicament, there are provided the aforementioned medicament which is used for preventive and/or therapeutic treatment of diseases caused by abnormal GSK3 $\beta$  activity, and the aforementioned medicament which is used for preventive and/or therapeutic treatment of neurodegenerative diseases and in addition other diseases such as: Non-insulin dependent diabetes (such as diabetes type II ) and obesity; manic depressive illness; schizophrenia; alopecia; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

As further preferred embodiments of the present invention, there are provided the aforementioned medicament wherein the diseases are neurodegenerative diseases and are selected from the group consisting of Alzheimer's disease, Parkinson's disease, tauopathies (e.g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration); brain and spinal cord trauma; peripheral neuropathies; retinopathies and glaucoma, and the aforementioned medicament in the form of pharmaceutical composition containing the above substance as an active ingredient together with one or more pharmaceutical additives.

The present invention further provides an inhibitor of GSK3 $\beta$  activity comprising as an active ingredient a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the salts thereof, and the solvates thereof and the hydrates thereof.



According to further aspects of the present invention, there are provided a method for preventive and/or therapeutic treatment of neurodegenerative diseases caused by abnormal GSK3 $\beta$  activity, which comprises the step of administering to a patient a preventively and/or therapeutically effective amount of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof; and a use of a substance selected from the group consisting of the pyrimidone derivatives of formula (I) and the physiologically acceptable salts thereof, and the solvates thereof and the hydrates thereof for the manufacture of the aforementioned medicament.

As used herein, the C<sub>1-6</sub> alkyl group represents a straight or branched alkyl group having 1 to 6 carbon atoms, for example, methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, tert-butyl group, n-pentyl group, isopentyl group, neopentyl group, 1,1-dimethylpropyl group, n-hexyl group, isohexyl group, and the like;

The C<sub>1-18</sub> alkyl group represents a straight or branched alkyl group having 1 to 18 carbon atoms, for example in addition to the C<sub>1-6</sub> alkyl group cited above, heptyl group, octyl group, nonyl group, decyl group, undecyl group, dodecyl group, tridecyl group, tetradecyl group, pentadecyl group, and octadecyl group;

The C<sub>3-8</sub> cycloalkyl group represents for example a cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group, and cyclooctyl group;

The C<sub>6,10</sub> aryl group represents a phenyl group, a naphth-1-yl group or a naphth-2-yl group;

The C<sub>7-20</sub> aralkyl group represents for example a benzyl group, phenylethyl group, phenylpropyl group, phenylbutyl group, naphthylmethyl group, naphthylethyl group, naphthylpropyl group, and naphthylbutyl group;

The C<sub>1-6</sub> alkoxy group represents an alkyl-oxy for example, methoxy group, ethoxy group, propoxy group, isopropoxy group, butoxy group, isobutoxy group, sec-butoxy group, tert-butoxy group, pentyloxy group, isopentyloxy group, neopentyloxy group, 1,1-dimethylpropyloxy group;

The C<sub>3-8</sub> cycloalkoxy group represents a cycloalkyl-oxy for example, cyclopropoxy group, cyclobutoxy group, cyclopentyloxy group, cyclohexyloxy group, cycloheptyloxy group, and cyclooctyloxy group, and the like;

The C<sub>7-20</sub> aralkyloxy group represents for example a benzyloxy group, phenylethyloxy group, phenylpropyloxy group, phenylbutoxy group, naphthylmethyloxy group, naphthylethyloxy group, naphthylpropyloxy group, and

naphthylbutyloxy group;

The C<sub>6-14</sub> aryloxy group represents for example a phenoxy group, and naphthoxy group;

5 The C<sub>1-6</sub> alkylthio group represents an alkyl-thio for example, methylthio group, ethylthio group, propylthio group, butylthio group and pentylthio group;

The C<sub>7-20</sub> aralkylthio group represents for example a benzylthio group, phenylethylthio group, phenylpropylthio group, phenylbutylthio group, naphthylmethylthio group, naphthylethylthio group, naphthylpropylthio group, and naphthylbutylthio group;

10 The C<sub>6-14</sub> arylthio group represents for example a phenylthio group, and naphththio group;

The halogen atom represents a fluorine, chlorine, bromine or iodine atom;

The C<sub>1-2</sub> perhalogenated alkyl group represents an alkyl group wherein all the hydrogen have been substituted by a halogeno, for example a CF<sub>3</sub> or C<sub>2</sub>F<sub>5</sub>,

15 The C<sub>1-3</sub> halogenated alkyl or (or C<sub>1-5</sub> halogenated alkyl group) represents an alkyl group wherein at least one hydrogen has not been substituted by a halogeno,

The C<sub>1-6</sub> alkylcarbonyl group represents for example a acetyl group, propionyl group, butyryl group, and valeryl group;

20 The C<sub>1-6</sub> monoalkylamino group represents an amino substituted by one C<sub>1-6</sub> alkyl group, for example, methylamino group, ethylamino group, propylamino group, isopropylamino group, butylamino group, isobutylamino group, tert-butylamino group, pentylamino group and isopentylamino group;

25 The C<sub>2-12</sub> dialkylamino group represents an amino substituted by two C<sub>1-6</sub> alkyl groups, for example, dimethylamino group, ethylmethylamino group, diethylamino group, methylpropylamino group and diisopropylamino group;

30 The (C<sub>1-6</sub> alkyl)carbonylamino group represents an amino group substituted by a C<sub>1-6</sub> acyl group, for example, formyl group, acetyl group, propionyl group, pivaloyl group, butyryl group, isobutyryl group, pentanoyl group, 3-methylbutyryl group, hexanoyl group;

The (C<sub>6,10</sub> aryl)carbonylamino group represents an amino group substituted by a benzoyl group or a naphthylenecarbonyl group;

35 The (C<sub>1-6</sub> alkoxy)carbonylamino group represents an amino group substituted with a (C<sub>1-6</sub> alkoxy)carbonyl group, such as for example, methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, *tert*-butoxycarbonyl group, pentyloxycarbonyl group, hexyloxycarbonyl group;

The C<sub>1-6</sub> monoalkylaminocarbonyl group represents an aminocarbonyl group substituted by one C<sub>1-6</sub> alkyl group, as defined and illustrated above, for example :

methylaminocarbonyl group, ethylaminocarbonyl group, propylaminocarbonyl group, *i*-propylaminocarbonyl group, butylaminocarbonyl group, *iso*-butylaminocarbonyl group, *tert*-butylaminocarbonyl group, pentylaminocarbonyl group, neopentylaminocarbonyl group, 1,1-dimethylpropylaminocarbonyl group, n-hexylaminocarbonyl group, isohexylaminocarbonyl group, and the like;

The C<sub>2-12</sub> dialkylaminocarbonyl group represents an aminocarbonyl group substituted by two C<sub>1-6</sub> alkyl groups, as defined and illustrated above, for example : dimethylaminocarbonyl group, diethylaminocarbonyl group, dipropylaminocarbonyl group, di-*i*-propylaminocarbonyl group, butylaminocarbonyl group, *iso*-butylaminocarbonyl group, *tert*-butylaminocarbonyl group, dipentylaminocarbonyl group, di-neopentylaminocarbonyl group, di-(1,1-dimethylpropyl)aminocarbonyl group, di-n-hexylaminocarbonyl group, di-isohexylaminocarbonyl group, ethylmethyaminocarbonyl group, ethylpropylaminocarbonyl group, ethyl-*tert*-butylaminocarbonyl group, and the like;

The C<sub>1-6</sub> alkylcarbonyl group represents an acyl group having 1 to 6 carbon atoms, such as, for example, formyl group, acetyl group, propionyl group, pivaloyl group, butyryl group, isobutyryl group, pentanoyl group, 3-methylbutyryl group, hexanoyl group;

The (C<sub>6,10</sub>-aryl)carbonyl group represents an arylcarbonyl group wherein the C<sub>6,10</sub> aryl group is as defined here above, such as, for example benzoyl group and a naphthylenecarbonyl group;

The C<sub>1-5</sub> alkylsulfonyl group represents an alkylsulfonyl group having 1 to 6 carbon atoms, such as, for example, methylsulfonyl group, ethylsulfonyl group, n-propylsulfonyl group, isopropylsulfonyl group, n-butyl group, isobutylsulfonyl group, sec-butylsulfonyl group, tert-butylsulfonyl group, n-pentylsulfonyl group, isopentylsulfonyl group, neopentylsulfonyl group, 1,1-dimethylpropylsulfonyl group;

The C<sub>6,10</sub> arylsulfonyl group represents an arylsulfonyl group wherein the C<sub>6,10</sub> aryl group is as defined here above, such as, for example, phenylsulfonyl group or naphthalenesulfonyl group;

The C<sub>1-6</sub> alkylsulfonylamino or C<sub>6,10</sub> arylsulfonylamino represents respectively a sulfonylamino group substituted by a C<sub>1-6</sub> alkyl or C<sub>6,10</sub> aryl group;

The C<sub>1-6</sub> monoalkylaminosulfonyl group represents an aminosulfonyl group substituted by one C<sub>1-6</sub> alkyl group, as defined and illustrated above, for example : methylaminosulfonyl group, ethylaminosulfonyl group, propylaminosulfonyl group, *i*-propylaminocarbonyl group, butylaminosulfonyl group, *iso*-butylaminosulfonyl group, *tert*-butylaminosulfonyl group, 1,1-dimethylpropylaminosulfonyl group, n-hexylaminosulfonyl group, isohexylaminosulfonyl group, and the like;

The C<sub>2-12</sub> dialkylaminosulfonyl group represents a aminosulfonyl group substituted by two C<sub>1-6</sub> alkyl group, as defined and illustrated above, for example : dimethylaminosulfonyl group, diethylaminosulfonyl group, dipropylaminosulfonyl group, *i*-propylaminocarbonyl group, butylaminosulfonyl group, *iso*-dibutylaminosulfonyl group, di-*tert*-butylaminosulfonyl group, di-(1,1-dimethylpropyl)aminosulfonyl group, di-*n*-hexylaminosulfonyl group, di-*iso*hexylaminosulfonyl group, ethylmethylaminocarbonyl group, ethylpropylaminocarbonyl group, ethyl-*tert*-butylaminocarbonyl group, and the like.

The heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5-10 represents a furan ring, dihydrofuran ring, tetrahydrofuran ring, pyran ring, dihydropyran ring, tetrahydropyran ring, benzofuran ring, furopyridine ring, isobenzofuran ring, chromene ring, chroman ring, isochroman ring, thiophene ring, benzothiophene ring, thienopyridine ring, pyrrole ring, pyrroline ring, pyrrolidine ring, imidazole ring, imidazoline ring, imidazolidine ring, imidazopyridine ring, pyrazole ring, pyrazoline ring, pyrazolidine ring, triazole ring, tetrazole ring, pyridine ring, pyridine oxide ring, piperidine ring, pyrazine ring, piperazine ring, pyrimidine ring, pyridazine ring, indolizine ring, indole ring, indoline ring, isoindole ring, isoindoline ring, indazole ring, benzimidazole ring, purine ring, quinolizine ring, quinoline ring, isoquinoline ring, phthalazine ring, naphthyridine ring, quinoxaline ring, quinazoline ring, cinnoline ring, pteridine ring, oxazole ring, oxazolidine ring, isoxazole ring, isoxazolidine ring, thiazole ring, benzothiazole ring, thiazylidine ring, isothiazole ring, isothiazolidine ring, dioxane ring, dithian ring, morpholine ring, thiomorpholine ring, phthalimide ring and the like.

The compounds represented by the aforementioned formula (I) may form a salt. Examples of the salt include, when an acidic group exists, salts of alkali metals and alkaline earth metals such as lithium, sodium, potassium, magnesium, and calcium; salts of ammonia and amines such as methylamine, dimethylamine, trimethylamine, dicyclohexylamine, tris(hydroxymethyl)aminomethane, N,N-bis(hydroxyethyl)piperazine, 2-amino-2-methyl-1-propanol, ethanolamine, N-methylglucamine, and L-glucamine; or salts with basic amino acids such as lysine,  $\delta$ -hydroxylysine, and arginine. The base-addition salts of acidic compounds are prepared by standard procedures well known in the art.

When a basic group exists, examples include salts with mineral acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid; salts with organic acids such as methanesulfonic acid, benzenesulfonic acid, p-

toluenesulfonic acid, acetic acid, propionic acid, tartaric acid, fumaric acid, maleic acid, malic acid, oxalic acid, succinic acid, citric acid, benzoic acid, mandelic acid, cinnamic acid, lactic acid, glycolic acid, glucuronic acid, ascorbic acid, nicotinic acid, and salicylic acid; or salts with acidic amino acids such as aspartic acid, and  
5 glutamic acid.

The acid-addition salts of the basic compounds are prepared by standard procedures well known in the art which include, but are not limited thereto, dissolving the free base in an aqueous alcohol solution containing the appropriate  
10 acid and isolating the salt by evaporating the solution, or by reacting the free base and an acid in an organic solvent, in which case the salt separates directly, or is precipitated with a second organic solvent, or can be obtained by concentration of the solution. The acids which can be used to prepare the acid-addition salts include preferably those which produce, when combined with the free base,  
15 pharmaceutically-acceptable salts, that is, salts whose anions are relatively innocuous to the animal organism in pharmaceutical doses of the salts, so that the beneficial properties inherent in the free base are not compromised by side effects ascribable to the anions. Although medicinally acceptable salts of the basic compounds are preferred, all acid-addition salts are within the scope of the  
20 present invention.

In addition to the pyrimidone derivatives represented by the aforementioned formula (I) and salts thereof, their solvates and hydrates also fall within the scope of the present invention. The pyrimidone derivatives represented  
25 by the aforementioned formula (I) may have one or more asymmetric carbon atoms. As for the stereochemistry of such asymmetric carbon atoms, they may independently be in either (R) and (S) configuration, and the pyrimidone derivative may exist as stereoisomers such as optical isomers, or diastereoisomers. Any stereoisomers in pure form, any mixtures of stereoisomers, racemates and the like  
30 fall within the scope of the present invention.

Furthermore, as the pyrimidone derivatives represented by the aforementioned formula (I), a 3H-4-one compound, a 4-hydroxy compound, and a 1H-4-one compound may exist as tautomers. The existence of such tautomers is  
35 readily apparent to those skilled in the art, and these tautomers fall within the scope of the present invention.

Examples of preferred compounds of the present invention are shown in

table 1 thereafter. However, the scope of the present invention is not limited by these compounds.

Preferred compounds of the present invention represented by formula (I) include  
5 also compounds wherein R<sub>3</sub> represents a 3- or 4-pyridyl group and more preferably 4-pyridyl group, which may be substituted by a C<sub>1-2</sub> alkyl, group, C<sub>1-2</sub> alkoxy group or a halogen atom.

More preferred compounds of the present invention represented by formula (I)  
10 include also

- (1) Compounds wherein R<sub>3</sub> represents a 4-pyridyl group which is unsubstituted.
- (2) Compounds wherein n represents 1 to 5, and more preferably 1 to 4.
- (3) When R<sub>1</sub> is an indole ring, compounds wherein n is 2.
- (4) When R<sub>1</sub> is an indole ring, compounds wherein the indole ring is unsubstituted  
15 or (A) is selected from a C<sub>1-6</sub> alkyl group, halogen atom, a C<sub>1-2</sub> perhalogenated alkyl group, a C<sub>1-3</sub> halogenated alkyl group, a hydroxyl group, a C<sub>1-6</sub> alkoxy group, methylenedioxy group, a nitro, a cyano, an amino, a C<sub>1-6</sub> monoalkylamino group, a C<sub>2-12</sub> dialkylamino group, a (C<sub>1-6</sub>-alkyl)carbonylamino group, a (C<sub>6,10</sub>-aryl)carbonylamino group, a (C<sub>1-6</sub>-alkoxy)carbonylamino group,  
20 aminocarbonyl group, a (C<sub>1-6</sub> monoalkylamino)carbonyl group, a (C<sub>2-12</sub> dialkylamino)carbonyl group, a formyl, a C<sub>1-6</sub> alkylcarbonyl group, a (C<sub>6,10</sub>-aryl)carbonyl group, a phenyl group, and a benzyloxy group, the alkyl or alkoxy group being unsubstituted; and preferably (A) is selected from a C<sub>1-6</sub> alkyl group preferably a methyl, ethyl or propyl group; a halogen, a C<sub>1-4</sub> alkoxy group  
25 and benzyloxy group.
- (5) When R<sub>1</sub> is an indole ring, compounds wherein R<sub>1</sub> is a 3-indolyl ring.
- (6) When R<sub>1</sub> is a furan ring, thiophene ring, pyrrole ring or imidazole ring, compounds wherein R<sub>1</sub> is unsubstituted or the substituent (A) is selected from  
30 a C<sub>1-6</sub> alkyl group, halogen atom, a C<sub>1-2</sub> perhalogenated alkyl group, a C<sub>1-3</sub> halogenated alkyl group, a hydroxyl group, a C<sub>1-6</sub> alkoxy group, methylenedioxy group, a nitro, a cyano, an amino, a C<sub>1-6</sub> monoalkylamino group, a C<sub>2-12</sub> dialkylamino group, a (C<sub>1-6</sub>-alkyl)carbonylamino group, and a (C<sub>6,10</sub>-aryl)carbonylamino group; and preferably compounds wherein R<sub>1</sub> is unsubstituted.
- (7) Compounds wherein R<sub>1</sub> represents furan ring, thiophene ring or imidazole ring.
- (8) When R<sub>1</sub> is a pyridine ring, compounds wherein R<sub>2</sub> is a hydrogen atom, a C<sub>1-5</sub> alkyl group optionally substituted by a phenyl group, preferably R<sub>2</sub> is a C<sub>1-3</sub> alkyl group optionally substituted by a phenyl group and more preferably a

methyl, ethyl or n-propyl optionally substituted by a phenyl group.

(9) When R1 is a pyridine ring, compounds wherein (B) is being selected from a C<sub>1-6</sub> alkyl group preferably methyl, ethyl or propyl group; a C<sub>1-6</sub> alkoxy group preferably methoxy, ethoxy or propoxy group; a halogen atom or an amino.

5 (10) Compounds wherein R1 represents a substituted phenyl group.

(11) Compounds wherein R2 represents a hydrogen atom or a unsubstituted C<sub>1-3</sub> alkyl group.

Particularly preferred compounds of the present invention represented by formula

10 (I) include :

- 2-[[[3,4-dimethoxyphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(4-methoxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(3-methoxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 15 2-[[[2-(2-methoxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(2-fluorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(3-fluorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(4-fluorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(4-bromophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 20 2-[[[2-(2,4-dichlorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(2-chlorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(4-chlorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(4-nitrophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(4-aminophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 25 2-[[[2-(3,4-dimethoxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(2,5-dimethoxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(4-hydroxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(4-methylphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(4-aminosulfonylphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 30 2-[[[2-(3-chlorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[4-(phenyl)butyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(4-phenylphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[2-(2-naphthyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[3-(aminomethyl)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 35 2-[[[4-(aminomethyl)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[3-(methylphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[4-(methoxyphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[4-(fluorophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,

- 2-[[[(2-chlorophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(4-chlorophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(4-(trifluoromethyl)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(4-(3-aminopropoxy)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
5 2-[[[(3,4-dimethoxyphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(3-nitrophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(2-aminophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(2-methylphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(4-methylphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
10 2-[[[(2-methoxyphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(3-methoxyphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(3-chlorophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(4-aminophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(3-(acetamidomethyl)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
15 2-[[[(3-(3-aminopropoxy)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(3-[(pyridin-2-yl)methoxy]phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-  
one,  
2-[[[(3-[3-(pyridin-3-yl)propoxy]phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-  
one,  
20 2-[[[(3-(*tert*-butyloxycarbonylaminomethyl)phenyl)methyl]amino]-6-pyridin-4-  
ylpyrimidin-4-(1H)-one,  
2-[[[(3-aminophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(3-(benzoylaminomethyl)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-  
one,  
25 2-[[[(4-(2-aminoethoxy)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(3-(methanesulfonylaminomethyl)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-  
4-(1H)-one,  
2-[[[(3-[(pyrimidin-2-yl)aminomethyl]phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-  
(1H)-one,  
30 2-[[[(3-(*n*-butylaminomethyl)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-  
one,  
2-[[[(3-(2-aminoethoxy)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(3-(4-aminobutoxy)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(3-(2-methylphenyl)propyl)amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
35 2-[[[(3-(3-methylphenyl)propyl)amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(3-(4-methylphenyl)propyl)amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(3-(2-methoxyphenyl)propyl)amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(3-(3-methoxyphenyl)propyl)amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,



- 2-[[3-(4-methoxyphenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[3-(2-chlorophenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[3-(3-chlorophenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[3-(4-chlorophenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 5 2-[[[3-[3-(pyridin-4-yl)propoxy]phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[3-[(pyridin-3-yl)methoxy]phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[3-[2-(pyridin-2-yl)ethoxy]phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 10 2-[[[3-(*tert*-butoxycarbonylamino)methyl]phenyl]methyl]methylamino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[3-(methylamino)phenyl]methyl]methylamino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 15 2-[[3-(3,4-dimethoxyphenyl)]propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[3-(4-phenylphenyl)]propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
  
 2-[[2-(1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,  
 2-[[2-(5-methoxy-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,  
 20 2-[[2-(5-methyl-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,  
 2-[[2-(5-benzyloxy-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,  
 2-[[2-(6-methoxy-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,  
 2-[[2-(6-fluoro-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,  
 2-[[2-(7-methyl-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,  
 25 2-[[2-[2-(1H-indol-3-yl)ethyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,  
 2-[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,  
 2-[[2-(1-methyl-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,  
  
 30 2-[(furan-3-yl-methyl)amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,  
 2-[[3-(1H-imidazol-1-yl)propyl]amino]-6-pyridin-4-ylpyrimidin-4(1H)-one, and  
 2-[2-(thiophen-2-yl-ethyl)amino]-6-pyridin-4-ylpyrimidin-4(1H)-one,  
  
 6-(4-pyridyl)-2-(2-(2-pyridyl)ethylamino)-3H- pyrimidin-4-one,  
 35 6-(4-pyridyl)-2-(2-(3-pyridyl)ethylamino)-3H- pyrimidin-4-one,  
 6-(4-pyridyl)-2-(2-(4-pyridyl)ethylamino)-3H- pyrimidin-4-one,  
 6-(4-pyridyl)-2-(3-(2-pyridyl)ethylamino)-3H- pyrimidin-4-one,  
 6-(4-pyridyl)-2-(3-(3-pyridyl)ethylamino)-3H- pyrimidin-4-one and

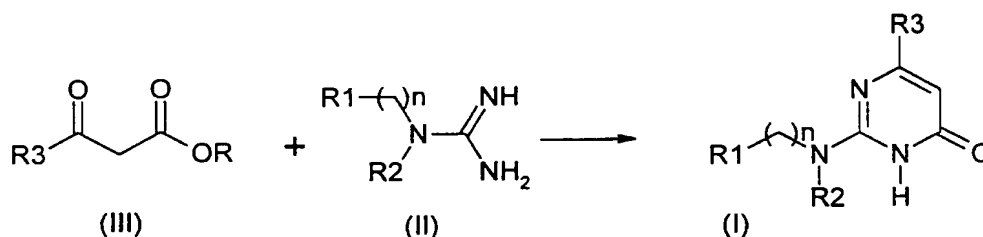
- 6-pyridin-4-yl-[(pyrid-2-ylmethyl)-amino]-3*H*-pyrimidin-4-one,  
 6-pyridin-4-yl-[(pyrid-3-ylmethyl)-amino]-3*H*-pyrimidin-4-one,  
 6-pyridin-4-yl-[(pyrid-4-ylmethyl)-amino]-3*H*-pyrimidin-4-one,  
 2-[methyl-(2-pyridin-2-yl-ethyl)-amino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one,  
 5 2-[benzyl-(2-pyridin-2-yl-ethyl)-amino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one,  
 2-(phenethyl-pyridin-3-ylmethyl-amino)-6-pyridin-4-yl-3*H*-pyrimidin-4-one,  
 2-[phenethyl-(2-pyridin-2-yl-ethyl)-amino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one,  
 n-{4-[(6-Oxo-4-pyridin-4-yl-1,6-dihydro-pyrimidin-2-yl)-phenethyl-amino]}-  
 10 butyl}acetamide,  
 n-{4-[(6-Oxo-4-pyridin-4-yl-1,6-dihydro-pyrimidin-2-yl)-phenethyl-amino]}-  
 butyl}methanesulfonamide  
 2-{benzyl-[2-(2-methoxy-phenyl)-ethyl]-amino}-6-pyridin-4-yl-3*H*-pyrimidin-4-one,  
 {4-[(6-Oxo-4-pyridin-4-yl-1,6-dihydro-pyrimidin-2-yl)-phenethyl-amino]-butyl}-  
 15 carbamic acid *tert*-butyl ester,  
 2-[(4-amino-butyl)-phenethyl-amino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one,  
 {4-[[2-(2-methoxy-phenyl)-ethyl]-(6-oxo-4-pyridin-4-yl-1,6-dihydro-pyrimidin-2-yl)-  
 amino]-butyl}-carbamic acid *tert*-butyl ester,  
 2-[(4-amino-butyl)-[2-(2-methoxy-phenyl)-ethyl]-amino]-6-pyridin-4-yl-3*H*-pyrimidin-  
 20 4-one,  
 2-[(4-hydroxy-butyl)-phenethyl-amino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one,  
 2-[(4-amino-butyl)-(3-phenyl-propyl)-amino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one,  
 2-(3-naphthalen-2-yl-propylamino)-6-pyridin-4-yl-3*H*-pyrimidin-4-one,  
 2-[2-(3-amino-propoxy)-benzylamino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one,  
 25 2-[2-(6-amino-hexyloxy)-benzylamino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one,  
 6-pyridin-4-yl-2-[2-(3-pyridin-4-yl-propoxy)-benzylamino]-3*H*-pyrimidin-4-one and  
 2-[(3-phenyl-propyl)-trifluoromethyl-amino]-6-pyridin-4-yl-3*H*-pyrimidin-4-one.

As a further object, the present invention concerns also methods for preparing the pyrimidone compounds represented by the aforementioned formula (I).

These compounds can be prepared, for example, according to methods explained below.

### 1. Preparation Method 1

scheme 1



(In the above scheme, R represents an alkyl group, which may be substituted, and definitions of R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, and n are the same as those already described for compound of formula (I).)

The 3-ketoester represented by the above formula (III) is allowed to react with the compound represented by formula (II) or a salt thereof to obtain the compound of the aforementioned formula (I) in the presence of a base such as lithium tert-butoxide, sodium tert-butoxide, potassium tert-butoxide, lithium methoxide, sodium methoxide, potassium methoxide, lithium ethoxide, sodium ethoxide, potassium ethoxide, 1,8-diazabicyclo[5,4,0]undec-7-ene, triethylamine, diisopropylethylamine, dimethylbenzylamine, dimethylaniline, diethylaniline and the like.

Examples of a solvent suitable for the reaction include, for example, alcoholic solvent such as methanol, ethanol, 1-propanol, isopropanol, tert-butanol; etheric solvents such as diethyl ether, tert-butyl methyl ether, tetrahydrofuran, isopropyl ether; hydrocarbon solvents such as benzene, toluene, xylene; halogenated solvents such as dichloromethane, chloroform, dichloroethane; aprotic polar solvents such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, dimethyl sulfoxide, sulfolane, hexamethylphosphoric triamide and the like. Generally, a single solvent or a mixture of two or more solvents may be used depending on the base used, and the reaction may be carried out for 1

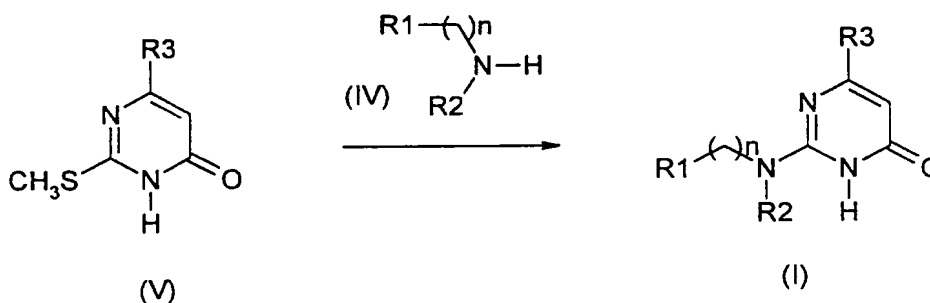
hour to 14 days at a suitable temperature ranging from 0° to 250°C under nitrogen or argon atmosphere or in ordinary air.

- Compounds of formula (III) and formula (II) are commercially available or may be synthesized according to known methods of one skilled in the art. For example compounds of formula (III), wherein R<sub>3</sub> represent a 4-pyridyl group optionally substituted by a C<sub>1-4</sub> alkyl group, C<sub>1-4</sub> alkoxy group or a halogen atom, can be prepared by reacting a nicotinic acid optionally substituted by a C<sub>1-4</sub> alkyl group, C<sub>1-4</sub> alkoxy group or an halogen, with a malonic acid monoester. The reaction can be carried out using methods well known to one skilled in the art, such as for example in presence of a coupling agent such as 1,1'-carbonylbis-1H-imidazole in a solvent such as a tetrahydrofuran at a temperature ranging from 20 to 70°C.

## 2. Preparation method 2

Alternatively pyrimidone compounds represented by the aforementioned formula (I) may be prepared according to scheme 2.

Scheme 2



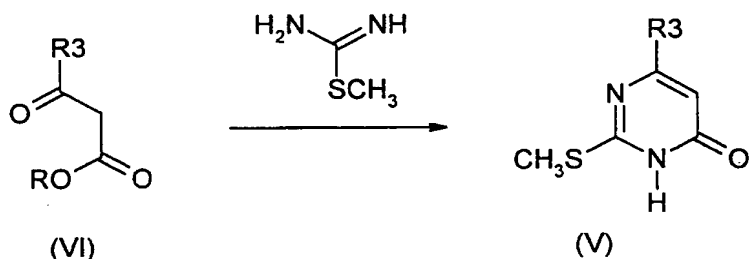
(In the above scheme the definition of R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and n are the same as those already described.)

- The 2-methylthio derivative represented by the above formula (V), wherein R<sub>3</sub> is as defined for compound of formula (I), is allowed to react with an amine of formula (IV) to obtain the compound of the aforementioned formula (I). The reaction may be carried out in a solvent such as, for example, an alcoholic solvent such as n-pentanol or isoamyl alcohol at a suitable temperature ranging from 100

to 180 °C under ordinary air.

Compound of formula (V) may be prepared according to the method defined in  
5 scheme 3.

Scheme 3



(In the above scheme the definition of  $\text{R}^3$  is the same as already  
10 described.)

According to this method, the 3-ketoester of formula (VI) is allowed to react with a  
2-methyl-2-thiopseudourea sulfate. The reaction may be carried out in solvent  
such as water or an alcohol, such as ethanol, propanol and butanol, at a suitable  
15 temperature ranging from 25-100°C under ordinary air.

Compounds of formula (IV) are commercially available or may be  
synthesized according to well-known methods of one skilled in the art.

20 In addition when applicable, compound of formula (I) could be derivatised  
into other compound of formula (I), using well known methods in the art. This is the  
case, for example, when  $\text{R}^1$  or a substituent on an alkyl or alkoxy group, could be  
oxidized, hydrogenated, alkylated..., or be transformed using well known method  
in the art to give another  $\text{R}^1$  group or a substituent within the scope of the present  
25 invention.

In the above reactions, protection or deprotection of a functional group  
may sometimes be necessary. A suitable protecting group can be chosen  
depending on the type of a functional group, and a method described in the  
30 literature may be applied. Examples of protecting groups, of protection and

deprotection methods are given for example in *Protective groups in Organic Synthesis* Greene et al., 2nd Ed. (John Wiley & Sons, Inc., New York).

5 The compounds of the present invention have inhibitory activity against GSK3 $\beta$ . Accordingly, the compounds of the present invention are useful as an active ingredient for the preparation of a medicament, which enables preventive and/or therapeutic treatment of neurodegenerative diseases such as Alzheimer's disease. In addition, the compounds of the present invention are also useful as an active ingredient for the preparation of a medicament for preventive and/or  
10 therapeutic treatment of neurodegenerative diseases such as Parkinson's disease, tauopathies (e.g. frontotemporoparietal dementia, corticobasal degeneration, Pick's disease, progressive supranuclear palsy) and other dementia including vascular dementia; acute stroke and others traumatic injuries; cerebrovascular accidents (e.g. age related macular degeneration); brain and spinal cord trauma;  
15 peripheral neuropathies; retinopathies and glaucoma; and other diseases such as non-insulin dependent diabetes (such as diabetes type II ) and obesity; manic depressive illness; schizophrenia; alopecia; cancers such as breast cancer, non-small cell lung carcinoma, thyroid cancer, T or B-cell leukemia and several virus-induced tumors.

20

The present invention further relates to a method for treating neurodegenerative diseases caused by abnormal activity of GSK3 $\beta$  and of the aforementioned diseases which comprises administering to a mammalian organism in need thereof an effective amount of a compound of the formula (I).

25

As the active ingredient of the medicament of the present invention, a substance may be used which is selected from the group consisting of the compound represented by the aforementioned formula (I) and pharmacologically acceptable salts thereof, and solvates thereof and hydrates thereof. The substance, per se,  
30 may be administered as the medicament of the present invention, however, it is desirable to administer the medicament in a form of a pharmaceutical composition which comprises the aforementioned substance as an active ingredient and one or more of pharmaceutical additives. As the active ingredient of the medicament of the present invention, two or more of the aforementioned substances may be used  
35 in combination. The above pharmaceutical composition may be supplemented with an active ingredient of another medicament for the treatment of the above mentioned diseases. A type of the pharmaceutical composition is not particularly limited, and the composition may be provided as any formulation for oral or

parenteral administration. For example, the pharmaceutical composition may be formulated, for example, in the form of pharmaceutical compositions for oral administration such as granules, fine granules, powders, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or in the form of pharmaceutical compositions for parenteral administrations such as injections for intravenous, intramuscular, or subcutaneous administration, drip infusions, transdermal preparations, transmucosal preparations, nasal drops, inhalants, suppositories and the like. Injections or drip infusions may be prepared as powdery preparations such as in the form of lyophilized preparations, and may be used by dissolving just before use in an appropriate aqueous medium such as physiological saline. Sustained-release preparations such as those coated with a polymer may be directly administered intracerebrally.

Types of pharmaceutical additives used for the manufacture of the pharmaceutical composition, content ratios of the pharmaceutical additives relative to the active ingredient, and methods for preparing the pharmaceutical composition may be appropriately chosen by those skilled in the art. Inorganic or organic substances, or solid or liquid substances may be used as pharmaceutical additives. Generally, the pharmaceutical additives may be incorporated in a ratio ranging from 1% by weight to 90% by weight based on the weight of an active ingredient.

Examples of excipients used for the preparation of solid pharmaceutical compositions include, for example, lactose, sucrose, starch, talc, cellulose, dextrin, kaolin, calcium carbonate and the like. For the preparation of liquid compositions for oral administration, a conventional inert diluent such as water or a vegetable oil may be used. The liquid composition may contain, in addition to the inert diluent, auxiliaries such as moistening agents, suspension aids, sweeteners, aromatics, colorants, and preservatives. The liquid composition may be filled in capsules made of an absorbable material such as gelatin. Examples of solvents or suspension mediums used for the preparation of compositions for parenteral administration, e.g. injections, suppositories, include water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecithin and the like. Examples of base materials used for suppositories include, for example, cacao butter, emulsified cacao butter, lauric lipid, witepsol.

Dose and frequency of administration of the medicament of the present invention are not particularly limited, and they may be appropriately chosen depending on conditions such as a purpose of preventive and/or therapeutic treatment, a type of a disease, the body weight or age of a patient, severity of a

disease and the like. Generally, a daily dose for oral administration to an adult may be 0.01 to 1,000 mg (the weight of an active ingredient), and the dose may be administered once a day or several times a day as divided portions, or once in several days. When the medicament is used as an injection, administrations may preferably be performed continuously or intermittently in a daily dose of 0.001 to 100 mg (the weight of an active ingredient) to an adult.

### Chemical Examples

The present invention will be explained more specifically with reference to the following general examples, however, the scope of the present invention is not limited to these examples.

Example 1 : preparation of 2-(arylalkylamino)-6-pyridin-4-ylpyrimidin-4(1H)-one or 2-(heteroarylalkylamino)-6-pyridin-4-ylpyrimidin-4(1H)-one.

#### 1.1. Preparation of Ethyl 3-(4-pyridyl)-3-oxopropionate

Isonicotinic acid (35.56 g, 289 mmol) was added to a solution of 1,1'-carbonylbis-1H-imidazole (46.98 g, 290 mmol) in tetrahydrofuran (700ml), and the resulting solution was stirred for 1.5 hr at 50°C. After cooling to room temperature, malonic acid monoester potassium salt (51.7 g, 304 mmol) and magnesium chloride (34.33 g, 361 mmol) were added, and the mixture was refluxed for 1 hr and then heated at 50°C for 6 hr. The solvent was removed under reduced pressure and the residue was quenched by the addition of dilute acetic acid. The organic layer was extracted with ethyl acetate (3 times) and the combined extracts were washed with dilute aqueous sodium bicarbonate and brine, and were concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent ; hexane/ethyl acetate = 2/1 to 1/1) and recrystallization from hexane – ethyl acetate gave 41.52 g (74%) of the title compound.

#### 1.2. Preparation of 2-(arylalkylamino)-6-pyridin-4-ylpyrimidin-4(1H)-one or 2-(heteroarylalkylamino)-6-pyridin-4-ylpyrimidin-4(1H)-one.

Ethyl 3-(4-pyridyl)-3-oxopropionate (0.60g ; 3.1mmol), compound of formula (II) (3.4 mmol) and potassium carbonate (1.15g ; 8.3mmol ) were added to 5 ml of ethanol, and the mixture was heated under reflux at 75° for 20 hours. Acetic acid was added to the reaction mixture , and the solvent was removed by distillation.



The residue was treated with water and then with acetic acid, and the resulting solid was separated by filtration, washed with water and ethyl acetate, and dried to obtain the desired compound.

5    2. Example 2 : Preparation of 2-(arylalkylamino)-6-pyridin-4-ylpyrimidin-4(1H)-one  
2-(heteroarylalkylamino)-6-pyridin-4-ylpyrimidin-4(1H)-one derivatives.

2.1. Preparation of 2-(Methylthio)-6-pyridinyl-4-ylpyrimidin-4(1H)-one

10    To a solution of 5.76 g (20.7 mmol) of 2-methyl-2-thiopseudoiurea sulfate in 48 ml of water was added 4.85 g (86.52 mmol) of potassium hydroxide. The mixture was agitated and 8.0 g (41.4 mmol) of ethyl 3-(4-pyridyl)-3-oxopropionate was added and stirring was maintained for 48 hours.

15    The precipitate was recovered by filtration and was washed with water and then ether. The product was dried at 90°C in vacuo to give 6.26 g, 69% of white solid.  
Mp : 328-330°C.

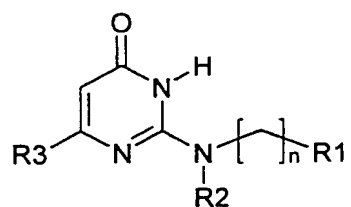
2.2 Preparation of 2-(arylalkylamino)-6-pyridin-4-ylpyrimidin-4(1H)-one or 2-(heteroarylalkylamino)-6-pyridin-4-ylpyrimidin-4(1H)-one derivatives

20    A solution of 1 equivalent of 2-(methylthio)-6-pyridinyl-4-ylpyrimidin-4(1H)-one of formula (V) and 3 to 5 equivalents of a compound of formula (IV) were suspended in amyl alcohol (0.1 - 0.2 M) and was heated at 150°C during 72 hours. The cooled solution was concentrated and purified by chromatography on silica gel.

25    Table 1 : a list of chemical structures and physical data for compounds of the aforementioned formula (I) illustrating the present invention is given in table 1.

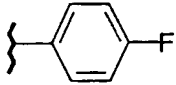
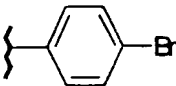
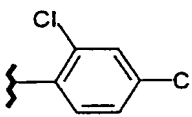
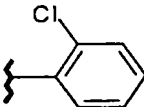
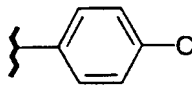
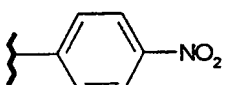
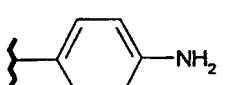
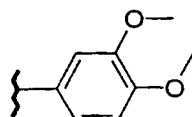
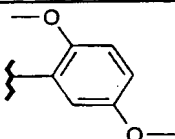
30    **Table 1 : ( on next pages)**

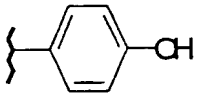
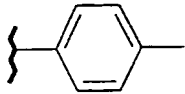
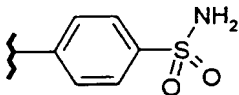
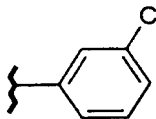
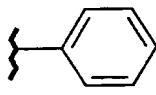
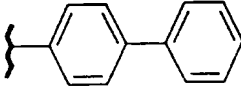
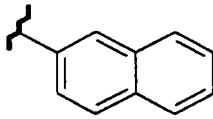
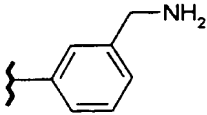
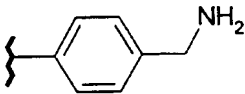
In the table Me represents a methyl group and R3 represents a 4-pyridyl.

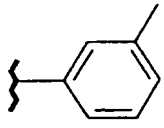
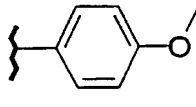
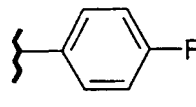
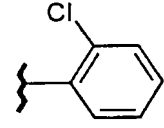
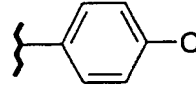
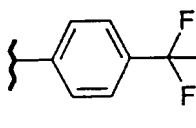
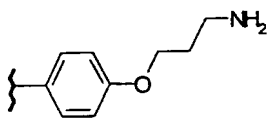
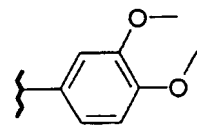
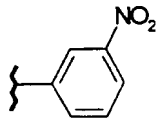


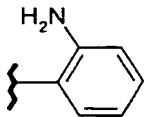
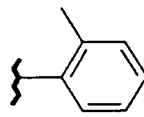
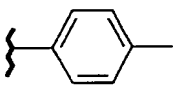
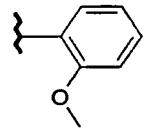
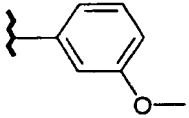
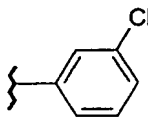
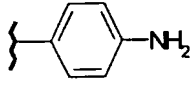
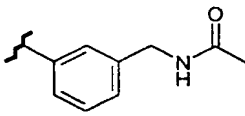
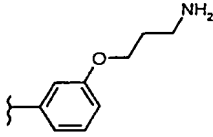
R3 = 4-Pyridyl

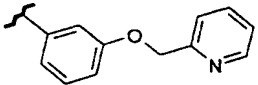
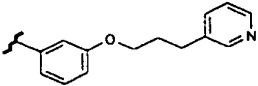
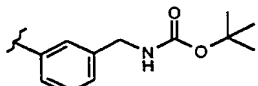
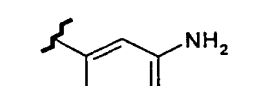
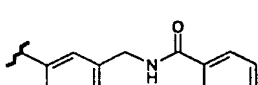
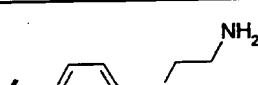
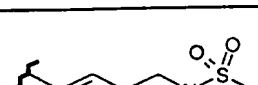
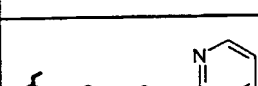
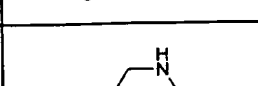
| No. | n | R1 | R2 | m.p. (°C)     | [M+H] <sup>+</sup> |
|-----|---|----|----|---------------|--------------------|
| 1   | 1 |    | H  | -             | 339                |
| 2   | 2 |    | Me | -             | 367                |
| 3   | 2 |    | H  | -             | 323                |
| 4   | 2 |    | H  | -             | 323                |
| 5   | 2 |    | H  | 200,3 - 200,5 | 323                |
| 6   | 2 |    | H  | 197,3 - 197,6 | 311                |
| 7   | 2 |    | H  | -             | 311                |

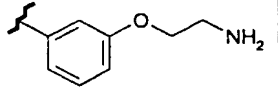
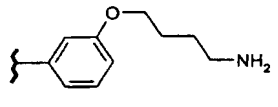
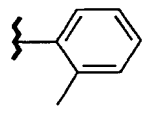
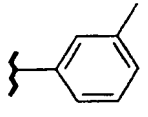
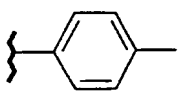
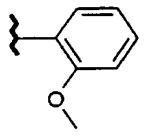
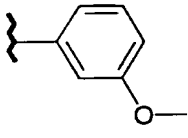
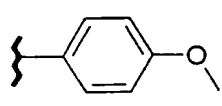
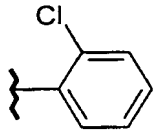
|    |   |   |   |               |     |
|----|---|---|---|---------------|-----|
| 8  | 2 |    | H | 195.0 - 195.3 | 311 |
| 9  | 2 |    | H | 241.5 - 241.8 | 372 |
| 10 | 2 |    | H | 238.0 - 238.4 | 362 |
| 11 | 2 |    | H | 216.7 - 216.9 | 327 |
| 12 | 2 |   | H | 213.8 - 214.1 | 327 |
| 13 | 2 |  | H | 223.9-224.1   | 338 |
| 14 | 2 |  | H | 221.7-221.8   | 308 |
| 15 | 2 |  | H | 152.8-153.2   | 353 |
| 16 | 2 |  | H | -             | 353 |

|    |   |   |   |               |     |
|----|---|---|---|---------------|-----|
| 17 | 2 |    | H | 228.8-229.1   | 309 |
| 18 | 2 |    | H | 247,7 - 247,9 | 307 |
| 19 | 2 |    | H | 245.6-245.8   | 372 |
| 20 | 2 |    | H | 180,8 - 181,0 | 327 |
| 21 | 4 |   | H | -             | 321 |
| 22 | 2 |  | H | -             | 369 |
| 23 | 2 |  | H | 208.5-208.7   | 343 |
| 24 | 1 |  | H | 245-250 (*)   | -   |
| 25 | 1 |  | H | 207-211 (*)   | -   |

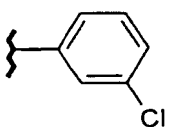
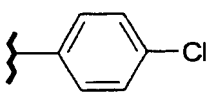
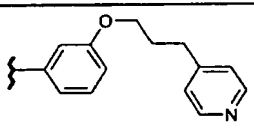
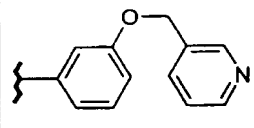
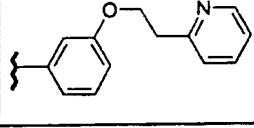
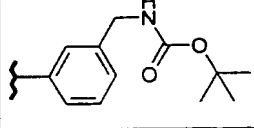
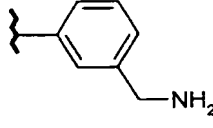
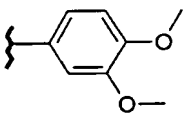
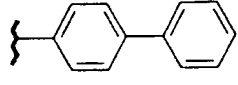
|    |   |   |   |             |   |
|----|---|---|---|-------------|---|
| 26 | 1 |    | H | 182-184     | - |
| 27 | 1 |    | H | 226-227     | - |
| 28 | 1 |    | H | 258-261     | - |
| 29 | 1 |    | H | 228-231     | - |
| 30 | 1 |   | H | 283-285     | - |
| 31 | 1 |  | H | 285-287     | - |
| 32 | 1 |  | H | 210-212 (*) | - |
| 33 | 1 |  | H | 166-168     | - |
| 34 | 1 |  | H | 239-242     | - |

|    |   |   |   |             |   |
|----|---|---|---|-------------|---|
| 35 | 1 |    | H | 231-232     | - |
| 36 | 1 |    | H | 236-240     | - |
| 37 | 1 |    | H | 252-255     | - |
| 38 | 1 |    | H | 204-207     | - |
| 39 | 1 |   | H | 181-182     | - |
| 40 | 1 |  | H | 203-205     | - |
| 41 | 1 |  | H | 178-181     | - |
| 42 | 1 |  | H | 267-270     | - |
| 43 | 1 |  | H | 182-184 (*) | - |

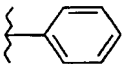
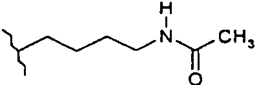
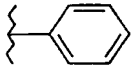
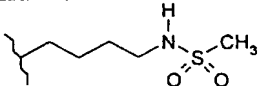
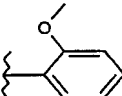
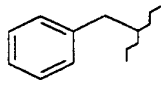
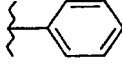
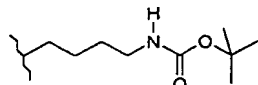
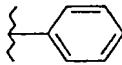
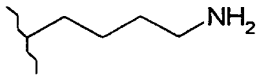
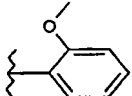
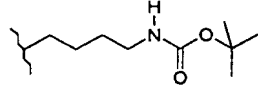
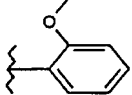
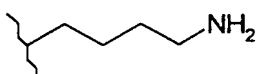
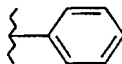
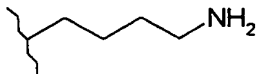
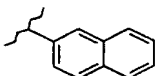
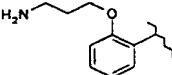
|    |   |   |   |             |   |
|----|---|---|---|-------------|---|
| 44 | 1 |    | H | 176-178     | - |
| 45 | 1 |    | H | 114-118 (*) | - |
| 46 | 1 |    | H | 202-205     | - |
| 47 | 1 |    | H | 208-212     | - |
| 48 | 1 |   | H | 136-140     | - |
| 49 | 1 |  | H | 210-212 (*) | - |
| 50 | 1 |  | H | 242-244     | - |
| 51 | 1 |  | H | 252-254     | - |
| 52 | 1 |  | H | 152-155 (*) | - |

|    |   |   |   |             |   |
|----|---|---|---|-------------|---|
| 53 | 1 |    | H | 202-204 (*) | - |
| 54 | 1 |    | H | 172-174 (*) | - |
| 55 | 3 |    | H | 162-163     | - |
| 56 | 3 |    | H | 147-149     | - |
| 57 | 3 |  | H | 204-206     | - |
| 58 | 3 |  | H | 135-137     | - |
| 59 | 3 |  | H | 143-144     | - |
| 60 | 3 |  | H | 205-207     | - |
| 61 | 3 |  | H | 157-159     | - |



|    |   |   |    |             |   |
|----|---|---|----|-------------|---|
| 62 | 3 |    | H  | 172-174     | - |
| 63 | 3 |    | H  | 211-213     | - |
| 64 | 1 |    | H  | 178-180     | - |
| 65 | 1 |    | H  | 172-173     | - |
| 66 | 1 |   | H  | 142-145 (*) | - |
| 67 | 1 |  | Me | 176-179     | - |
| 68 | 1 |  | Me | 191-195 (*) | - |
| 69 | 3 |  | H  | 178-180     | - |
| 70 | 3 |  | H  | 189-191     | - |

All compounds are bases, except (\*) = dihydrochloride

|    |   |   |  |            |
|----|---|---|--|------------|
| 71 | 2 |    |    | 235-242    |
| 72 | 2 |    |    | amorphous  |
| 73 | 2 |    |    | 200-202    |
| 74 | 2 |    |    | 159-162    |
| 75 | 2 |    |    | 270-272(*) |
| 76 | 2 |   |    | 142-144    |
| 77 | 2 |  |  | 240-242(*) |
| 78 | 3 |  |  | 229-232(*) |
| 79 | 3 |  | H  | 219-221    |
| 80 | 1 |  | H  | 189-190(*) |

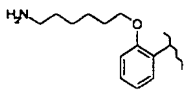
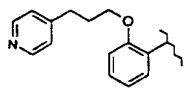
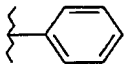
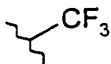
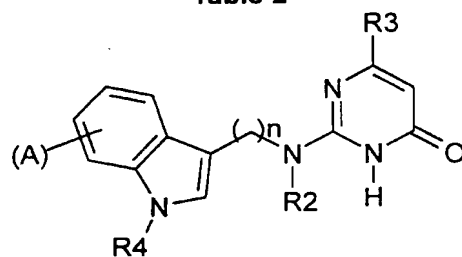
|    |   |   |  |            |
|----|---|---|--|------------|
| 81 | 1 |  | H  | 150-155(*) |
| 82 | 1 |  | H  | 163-166    |
| 83 | 3 |  |  | 224-226    |

Table 2

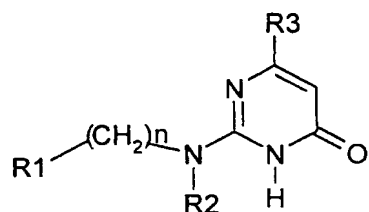


5

| No. | n | R <sub>4</sub>  | R <sub>2</sub> | (A)  | m.p. (°C)   | [M+H] <sup>+</sup> |
|-----|---|-----------------|----------------|--|-------------|--------------------|
| 1   | 2 | H               | H              | H  | 206-208 (*) | 332                |
| 2   | 2 | H               | H              | 5-OCH <sub>3</sub>                               | 166.8-166.9 | 362                |
| 3   | 2 | H               | H              | 5-CH <sub>3</sub>                                | -           | 346                |
| 4   | 2 | H               | H              | 5-OCH <sub>2</sub> C <sub>6</sub> H <sub>5</sub> | -           | 438                |
| 5   | 2 | H               | H              | 6-OCH <sub>3</sub>                               | -           | 362                |
| 6   | 2 | H               | H              | 6-F  | 223.3-223.5 | 350                |
| 7   | 2 | H               | H              | 7-CH <sub>3</sub>                                | 174.7-174.8 | 346                |
| 8   | 2 | H               | Me             | H  | 207-207.3   | 346                |
| 9   | 2 | H               | H              | 2-CH <sub>3</sub>                                | -           | 346                |
| 10  | 2 | CH <sub>3</sub> | H              | H  | -           | 346                |

all compounds of the table are bases , except (\*) which is an oxalate

Table 3



(I)

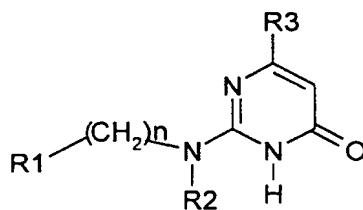
R3 is an unsubstituted 4-pyridyl group

5

| No. | n | R2 | R1 | m.p. (°C)     | [M+H] <sup>+</sup> |
|-----|---|----|----|---------------|--------------------|
| 1   | 1 | H  |    | -             | 269                |
| 2   | 3 | H  |    | -             | 297                |
| 3   | 2 | H  |    | 193,6 - 193,8 | 299                |

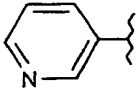
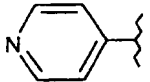
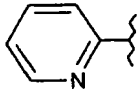
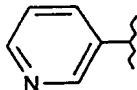
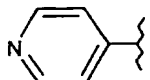
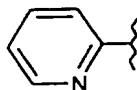
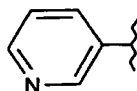
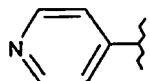
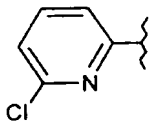
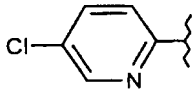
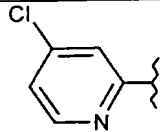
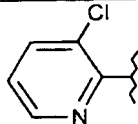
10

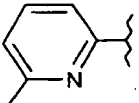
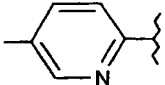
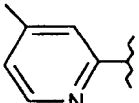
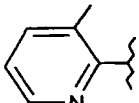
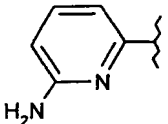
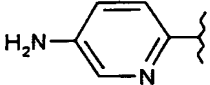
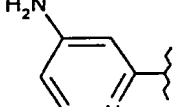
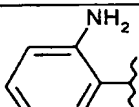
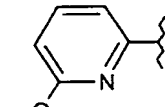
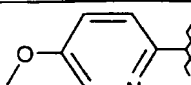
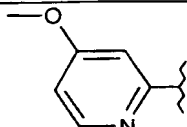
Table 4



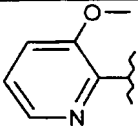
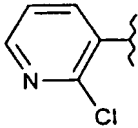
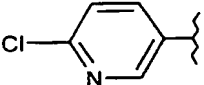
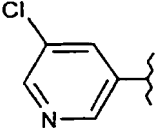
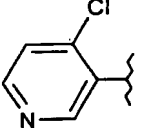
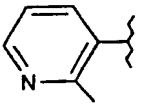

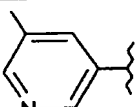
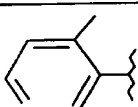
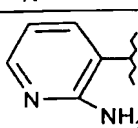
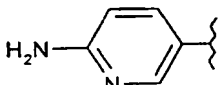
(I)

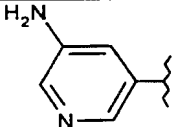
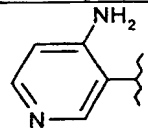
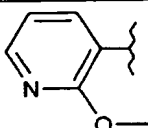
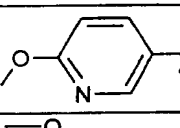
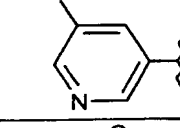
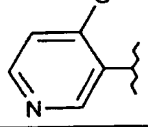
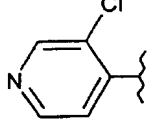
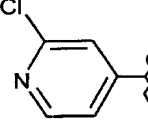
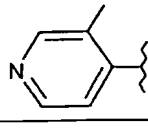
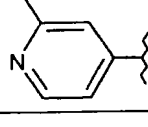
| N° | n | R <sub>1</sub> | R <sub>2</sub>  | m.p.(°C) |
|----|---|----------------|-----------------|----------|
| 1  | 1 |                | H               | 238-239  |
| 2  | 1 |                | H               | 277-279  |
| 3  | 1 |                | H               | 234-237  |
| 4  | 1 |                | CH <sub>3</sub> |          |
| 5  | 1 |                | CH <sub>3</sub> |          |
| 6  | 1 |                | CH <sub>3</sub> |          |
| 7  | 2 |                | H               | 197-199  |
| 8  | 2 |                | H               |          |
| 9  | 2 |                | H               | 199-202  |
| 10 | 2 |                | CH <sub>3</sub> | 213-217  |

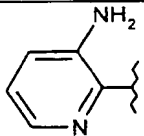
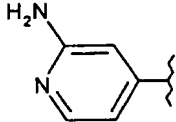
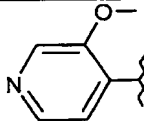
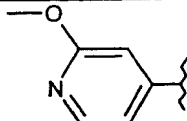
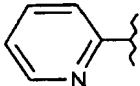
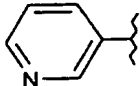
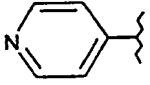
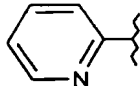
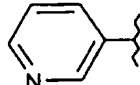
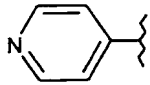
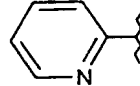
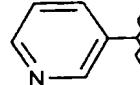
| N° | n | R <sub>1</sub>  | R <sub>2</sub>                                  | m.p.(°C) |
|----|---|---|---|----------|
| 11 | 2 |    | CH <sub>3</sub>                                 |          |
| 12 | 2 |    | CH <sub>3</sub>                                 |          |
| 13 | 2 |    | CH <sub>2</sub> CH <sub>3</sub>                 |          |
| 14 | 2 |    | CH <sub>2</sub> CH <sub>3</sub>                 |          |
| 15 | 2 |    | (CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub> |          |
| 16 | 2 |    | (CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub> |          |
| 17 | 2 |  | (CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub> |          |
| 18 | 2 |  | CH <sub>2</sub> CH <sub>3</sub>                 |          |
| 19 | 2 |  | H   |          |
| 20 | 2 |  | H   |          |
| 21 | 2 |  | H   |          |
| 22 | 2 |  | H   |          |

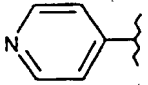
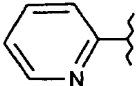
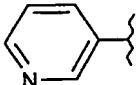
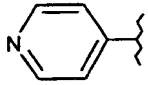
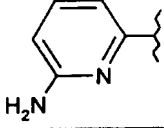
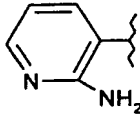
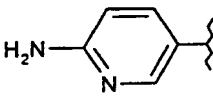
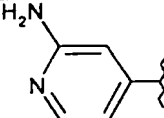
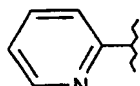
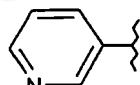
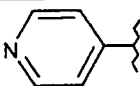
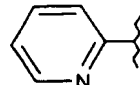
| N° | n | R <sub>1</sub>  | R <sub>2</sub> | m.p.(°C) |
|----|---|---|----------------|----------|
| 23 | 2 |    | H              |          |
| 24 | 2 |    | H              |          |
| 25 | 2 |    | H              |          |
| 26 | 2 |    | H              |          |
| 27 | 2 |    | H              |          |
| 28 | 2 |  | H              |          |
| 29 | 2 |  | H              |          |
| 30 | 2 |  | H              |          |
| 31 | 2 |  | H              |          |
| 32 | 2 |  | H              |          |
| 33 | 2 |  | H              |          |

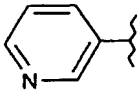
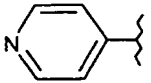
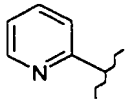
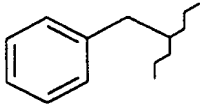
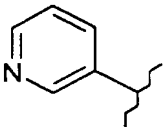
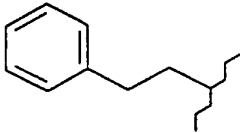
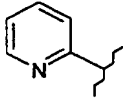
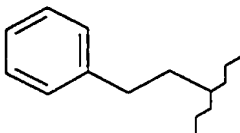


| N° | n | R <sub>1</sub>  | R <sub>2</sub> | m.p.(°C) |
|----|---|---|----------------|----------|
| 34 | 2 |    | H              |          |
| 35 | 2 |    | H              |          |
| 36 | 2 |    | H              |          |
| 37 | 2 |    | H              |          |
| 38 | 2 |   | H              |          |
| 39 | 2 |  | H              |          |
| 40 | 2 |  | H              |          |
| 41 | 2 |  | H              |          |
| 42 | 2 |  | H              |          |
| 43 | 2 |  | H              |          |
| 44 | 2 |  | H              |          |

| N° | n | R <sub>1</sub>  | R <sub>2</sub> | m.p.(°C) |
|----|---|---|----------------|----------|
| 45 | 2 |    | H              |          |
| 46 | 2 |    | H              |          |
| 47 | 2 |    | H              |          |
| 48 | 2 |    | H              |          |
| 49 | 2 |   | H              |          |
| 50 | 2 |  | H              |          |
| 51 | 2 |  | H              |          |
| 52 | 2 |  | H              |          |
| 53 | 2 |  | H              |          |
| 54 | 2 |  | H              |          |

| N° | n | R <sub>1</sub>  | R <sub>2</sub>  | m.p.(°C) |
|----|---|---|-----------------|----------|
| 55 | 2 |    | H               |          |
| 56 | 2 |    | H               |          |
| 57 | 2 |    | H               |          |
| 58 | 2 |    | H               |          |
| 59 | 3 |   | H               |          |
| 60 | 3 |  | H               | 165-170  |
| 61 | 3 |  | H               |          |
| 62 | 3 |  | CH <sub>3</sub> |          |
| 63 | 3 |  | CH <sub>3</sub> |          |
| 64 | 3 |  | CH <sub>3</sub> |          |
| 65 | 4 |  | H               |          |
| 66 | 4 |  | H               |          |

| N° | n | R <sub>1</sub>  | R <sub>2</sub>  | m.p.(°C) |
|----|---|---|-----------------|----------|
| 67 | 4 |    | H               |          |
| 68 | 4 |    | CH <sub>3</sub> |          |
| 69 | 4 |    | CH <sub>3</sub> |          |
| 70 | 4 |    | CH <sub>3</sub> |          |
| 71 | 3 |    | H               |          |
| 72 | 3 |   | H               |          |
| 73 | 3 |  | H               |          |
| 74 | 3 |  | H               |          |
| 75 | 5 |  | H               |          |
| 76 | 5 |  | H               |          |
| 77 | 5 |  | H               |          |
| 78 | 5 |  | CH <sub>3</sub> |          |

| N° | n | R <sub>1</sub>   | R <sub>2</sub>  | m.p.(°C) |
|----|---|--|---|----------|
| 79 | 5 |   | CH <sub>3</sub>   |          |
| 80 | 5 |   | CH <sub>3</sub>   |          |
| 81 | 2 |   |   | 181-183  |
| 82 | 1 |   |   | 248-250  |
| 83 | 2 |  |  | 204-206  |

**Test Example: Inhibitory activity of the medicament of the present invention against GSK3 $\beta$ :**

Two different protocols can be used.

5

In a first protocol : 7.5  $\mu$ M of prephosphorylated GS1 peptide and 10  $\mu$ M ATP (containing 300,000 cpm of 33P-ATP) were incubated in 25 mM Tris-HCl, pH 7.5, 0.6 mM DTT, 6 mM MgCl<sub>2</sub>, 0.6 mM EGTA, 0.05 mg/ml BSA buffer for 1 hour at room temperature in the presence of GSK3 $\beta$  (total reaction volume : 100 microliters).

10

In a second protocol : 4.1  $\mu$ M of prephosphorylated GS1 peptide and 42  $\mu$ M ATP (containing 260,000 cpm 33P-ATP) were incubated in 80 mM Mes-NaOH, pH 6.5, 1 mM Mg acetate, 0.5 mM EGTA, 5 mM 2-mercaptoethanol, 0.02% Tween 20, 10% glycerol buffer for 2 hours at room temperature in the presence of GSK3 $\beta$ . Inhibitors were solubilised in DMSO (final solvent concentration in the reaction medium, 1%).

15

The reaction was stopped with 100 microliters of a solution made of 25 g polyphosphoric acid (85% P<sub>2</sub>O<sub>5</sub>), 126 ml 85% H<sub>3</sub>PO<sub>4</sub>, H<sub>2</sub>O to 500 ml and then diluted to 1 :100 before use. An aliquot of the reaction mixture was then transferred to Whatman P81 cation exchange filters and rinsed with the solution described above. Incorporated 33P radioactivity was determined by liquid scintillation spectrometry.

20

The phosphorylated GS-1 peptide had the following sequence :  
NH<sub>2</sub>-YRRAAVPPSPSLSRHSSPHQS(P)EDEE-COOH.

25

The GSK3 $\beta$  inhibitory activity of the compounds of the present invention are expressed in IC<sub>50</sub>, and, as an illustration the range of IC<sub>50</sub>'s for the compounds in table 1 is between 0,01 to 10 micromolar concentrations.

30

### Formulation Example

#### (1) Tablets

5       The ingredients below were mixed by an ordinary method and  
compressed by using a conventional apparatus.

Compound of Example 1 30 mg

Crystalline cellulose 60 mg

Corn starch 100 mg

Lactose 200 mg

10    Magnesium stearate 4 mg

#### (2) Soft capsules

      The ingredients below were mixed by an ordinary method and filled in soft  
capsules.

15    Compound of Example 1 30 mg

Olive oil 300 mg

Lecithin 20 mg

#### (1) Parenteral preparations

20

      The ingredients below were mixed by an ordinary method to prepare  
injections contained in a 1 ml ampoule.

Compound of Example 13 mg

Sodium chloride 4 mg

25    Distilled water for injection 1 ml

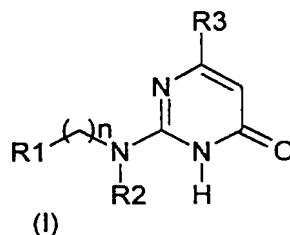
### Industrial Applicability

30       The compounds of the present invention have GSK3 $\beta$  inhibitory activity  
and are useful as an active ingredient of a medicament for preventive and/or  
therapeutic treatment of neurodegenerative diseases caused by abnormal activity  
of GSK3 $\beta$ .

What is claimed is:

1. A pyrimidone derivative represented by formula (I) or a salt thereof, or a solvate thereof or a hydrate thereof:

5



wherein:

R2 represents a hydrogen atom, a C<sub>1-2</sub> perhalogenated alkyl group or a C<sub>1-6</sub> alkyl group which may be substituted by 1 to 3 groups selected from a halogen atom, an amino, a (C<sub>1-6</sub>-alkyl)carbonylamino group, a (C<sub>1-6</sub>-alkoxy)carbonylamino group, a C<sub>1-6</sub> alkylsulfonylamino group or a phenyl group;

10

R3 represents a 2, 3 or 4-pyridyl group optionally substituted by a C<sub>1-4</sub> alkyl, group, C<sub>1-4</sub> alkoxy group or a halogen atom; and

15

- ◆ When n represents 1 to 10, then R1 represents
    - an unsubstituted naphth-1-yl group;
    - an unsubstituted naphth-2-yl group;
    - a C<sub>6,10</sub> aryl group substituted by 1 to 3 substituents (A);
    - a furan ring, thiophene ring, pyrrole ring or imidazole ring, the rings being optionally substituted by 1 to 3 substituents (A);
    - an indole ring, attached by a carbon atom, optionally substituted by 1 to 3 substituents (A), the nitrogen of the indole ring being optionally substituted by a C<sub>1-6</sub> alkyl group;
- 20
- the substituent (A) being selected from a C<sub>1-6</sub> alkyl group, halogen atom, a C<sub>1-2</sub> perhalogenated alkyl group, a C<sub>1-3</sub> halogenated alkyl group, a hydroxyl group, a C<sub>1-6</sub> alkoxy group, methylenedioxy group, a nitro, a cyano, an amino, a C<sub>1-6</sub> monoalkylamino group, a C<sub>2-12</sub> dialkylamino group, a (C<sub>1-6</sub>-alkyl)carbonylamino group, a (C<sub>6,10</sub>-aryl)carbonylamino group, a (C<sub>1-6</sub>-alkoxy)carbonylamino group, aminocarbonyl group, a (C<sub>1-6</sub> monoalkylamino)carbonyl group, a (C<sub>2-12</sub> dialkylamino)carbonyl group, a
- 25
- 30



formyl, a C<sub>1-6</sub> alkylcarbonyl group, a (C<sub>6,10</sub>-aryl)carbonyl group, a C<sub>1-5</sub> alkylsulfonyl group, a C<sub>6,10</sub> arylsulfonyl group, an aminosulfonyl group, a C<sub>1-6</sub> monoalkylaminosulfonyl group, a C<sub>2-12</sub> dialkylaminosulfonyl group, a phenyl group or a benzyloxy group;

5 the C<sub>1-6</sub> alkyl groups and the C<sub>1-6</sub> alkoxy groups being optionally substituted by a halogen atom, a hydroxyl group, a C<sub>1-6</sub> alkoxy group, an amino, a C<sub>1-6</sub> monoalkylamino group, a C<sub>2-12</sub> dialkylamino group, a (C<sub>1-6</sub> alkyl)carbonylamino group, a (C<sub>6,10</sub> aryl)carbonylamino group, a (C<sub>1-6</sub> alkoxy)carbonylamino group, a C<sub>1-6</sub> alkylsulfonylamino group, a C<sub>6,10</sub> arylsulfonylamino group, a phenyl group, a pyridine, a pyrimidine, or a pyrimidin-2-yl-amino;

- a pyridine ring optionally substituted by 1 to 3 substituents (B);

15 the substituent (B) being selected from a C<sub>1-18</sub> alkyl group, a C<sub>3-8</sub> cycloalkyl group, a C<sub>7-20</sub> aralkyl group, a C<sub>6-10</sub> aryl group, a fluorenyl group, a C<sub>1-6</sub> alkoxy group, a C<sub>3-8</sub> cycloalkyloxy group, a C<sub>7-20</sub> aralkyloxy group, a C<sub>6-14</sub> aryloxy group, a C<sub>1-5</sub> alkylthio group, a C<sub>7-20</sub> aralkylthio group, a C<sub>6-14</sub> arylthio group, a C<sub>1-5</sub> alkylsulfonyl group, a C<sub>6,10</sub> arylsulfonyl group, a halogen atom, a C<sub>1-2</sub> perhalogenated alkyl group, a C<sub>1-5</sub> halogenated alkyl group, a hydroxyl group, a cyano, a nitro, an oxo group, a formyl group, a C<sub>1-6</sub> alkylcarbonyl group, a (C<sub>6,10</sub>-aryl)carbonyl group, an amino, a C<sub>1-5</sub> monoalkylamino group, a C<sub>2-10</sub> dialkylamino group, or a heterocyclic ring having 1-4 hetero atoms selected from oxygen atom, sulfur atom, and nitrogen atom, and having total ring-constituting atoms of 5-10;

25

- ♦ When n represents 4 to 10 then R1 can represent in addition an unsubstituted phenyl group; and

30 ♦ When n represents 1 to 3 and R1 represents an unsubstituted phenyl group then R2 represents a C<sub>1-2</sub> perhalogenated alkyl group or a C<sub>1-6</sub> alkyl substituted by 1 to 3 groups selected from a halogen atom, an amino, a (C<sub>1-6</sub>-alkyl)carbonylamino group, a (C<sub>1-6</sub>-alkoxy)carbonylamino group and a C<sub>1-6</sub> alkylsulfonylamino group.

35 2. A pyrimidone derivative or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 2, wherein R3 is an unsubstituted 4-pyridyl group.

3. A pyrimidone derivative or a salt thereof, or a solvate thereof or a hydrate thereof according to claim 2, wherein n represents 1 to 4

4. A pyrimidone derivative which is selected from the group consisting of :
- 2-[[[(3,4-dimethoxyphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[2-(3,4-dimethoxyphenyl)ethyl]methylamino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
5 2-[[2-(4-methoxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[2-(3-methoxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[2-(2-methoxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[2-(2-fluorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[2-(3-fluorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
10 2-[[2-(4-fluorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[2-(4-bromophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[2-(2,4-dichlorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[2-(2-chlorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[2-(4-chlorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
15 2-[[2-(4-nitrophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[2-(4-aminophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[2-(3,4-dimethoxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[2-(2,5-dimethoxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[2-(4-hydroxyphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
20 2-[[2-(4-methylphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[2-(4-aminosulfonylphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[2-(3-chlorophenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[4-(phenyl)butyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[2-(4-phenylphenyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
25 2-[[2-(2-naphthyl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-(aminomethyl)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[4-(aminomethyl)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-(methylphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[4-(methoxyphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
30 2-[[[4-(fluorophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[2-(chlorophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[4-(chlorophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[4-(trifluoromethyl)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[4-(3-aminopropoxy)phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
35 2-[[[(3,4-dimethoxyphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(3-nitrophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(2-aminophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(2-methylphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,

- 2-[[[4-methylphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(2-methoxyphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(3-methoxyphenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(3-chlorophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
5 2-[[[(4-aminophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-(acetamidomethyl)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-(3-aminopropoxy)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-[(pyridin-2-yl)methoxy]phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
10 2-[[[3-[3-(pyridin-3-yl)propoxy]phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-(*tert*-butoxycarbonylaminomethyl)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[(3-aminophenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
15 2-[[[3-(benzoylaminomethyl)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[4-(2-aminoethoxy)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-(methanesulfonylaminomethyl)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
20 2-[[[3-[(pyrimidin-2-yl)aminomethyl]phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-(*n*-butylaminomethyl)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-(2-aminoethoxy)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
25 2-[[[3-(4-aminobutoxy)phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-(2-methylphenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-(3-methylphenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-(4-methylphenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-(2-methoxyphenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
30 2-[[[3-(3-methoxyphenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-(4-methoxyphenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-(2-chlorophenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-(3-chlorophenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-(4-chlorophenyl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
35 2-[[[3-[3-(pyridin-4-yl)propoxy]phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
2-[[[3-[(pyridin-3-yl)methoxy]phenyl)methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,

- 2-[[[3-{2-(pyridin-2-yl)ethoxy}phenyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[[3-(*tert*-butoxycarbonylaminomethyl)phenyl]methyl]methylamino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 5 2-[[[3-(methylamino)phenyl]methyl]methylamino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[3-(3,4-dimethoxyphenyl)]propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[3-(4-phenylphenyl)]propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 10 2-[[2-(1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[2-(5-methoxy-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[2-(5-methyl-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[2-(5-benzyloxy-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[2-(6-methoxy-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 15 2-[[2-(6-fluoro-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[2-(7-methyl-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[2-[2-(1H-indol-3-yl)ethyl]methyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[2-(2-methyl-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[2-(1-methyl-1H-indol-3-yl)ethyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 20  
 2-[(furan-3-yl-methyl)amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 2-[[3-(1H-imidazol-1-yl)propyl]amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one, and  
 2-[2-(thiophen-2-yl-ethyl)amino]-6-pyridin-4-ylpyrimidin-4-(1H)-one,  
 25  
 6-(4-pyridyl)-2-(2-(2-pyridyl)ethylamino)-3H-pyrimidin-4-one,  
 6-(4-pyridyl)-2-(2-(3-pyridyl)ethylamino)-3H-pyrimidin-4-one,  
 6-(4-pyridyl)-2-(2-(4-pyridyl)ethylamino)-3H-pyrimidin-4-one,  
 6-(4-pyridyl)-2-(3-(2-pyridyl)ethylamino)-3H-pyrimidin-4-one,  
 30 6-(4-pyridyl)-2-(3-(3-pyridyl)ethylamino)-3H-pyrimidin-4-one and  
 6-(4-pyridyl)-2-(3-(4-pyridyl)ethylamino)-3H-pyrimidin-4-one,  
 2-[Benzyl-(2-pyridin-2-yl-ethyl)-amino]-6-pyridin-4-yl-3H-pyrimidin-4-one,  
 2-(Phenethyl-pyridin-3-ylmethyl-amino)-6-pyridin-4-yl-3H-pyrimidin-4-one,  
 2-[Phenethyl-(2-pyridin-2-yl-ethyl)-amino]-6-pyridin-4-yl-3H-pyrimidin-4-one,  
 35 N-[4-[(6-Oxo-4-pyridin-4-yl-1,6-dihydro-pyrimidin-2-yl)-phenethyl-amino]]-butyl]acetamide  
 N-[4-[(6-Oxo-4-pyridin-4-yl-1,6-dihydro-pyrimidin-2-yl)-phenethyl-amino]-butyl]methanesulfonamide

- 2-{Benzyl-[2-(2-methoxy-phenyl)-ethyl]-amino}-6-pyridin-4-yl-3H-pyrimidin-4-one,  
 {4-[(6-Oxo-4-pyridin-4-yl-1,6-dihydro-pyrimidin-2-yl)-phenethyl-amino]-butyl}-  
 carbamic acid *tert*-butyl ester  
 2-[(4-Amino-butyl)-phenethyl-amino]-6-pyridin-4-yl-3H-pyrimidin-4-one,  
 5 {4-[[2-(2-Methoxy-phenyl)-ethyl]-(6-oxo-4-pyridin-4-yl-1,6-dihydro-pyrimidin-2-yl)-  
 amino]-butyl}-carbamic acid *tert*-butyl ester  
 2-[(4-Amino-butyl)-[2-(2-methoxy-phenyl)-ethyl]-amino]-6-pyridin-4-yl-3H-  
 pyrimidin-4-one,  
 2-[(4-Hydroxy-butyl)-phenethyl-amino]-6-pyridin-4-yl-3H-pyrimidin-4-one,  
 10 2-[(4-Amino-butyl)-(3-phenyl-propyl)-amino]-6-pyridin-4-yl-3H-pyrimidin-4-one,  
 2-(3-Naphthalen-2-yl-propylamino)-6-pyridin-4-yl-3H-pyrimidin-4-one,  
 2-[2-(3-Amino-propoxyl)-benzylamino]-6-pyridin-4-yl-3H-pyrimidin-4-one,  
 2-[2-(6-Amino-hexyloxy)-benzylamino]-6-pyridin-4-yl-3H-pyrimidin-4-one,  
 6-Pyridin-4-yl-2-[2-(3-pyridin-4-yl-propoxy)-benzylamino]-3H-pyrimidin-4-one,  
 15 2-[(3-Phenyl-propyl)-trifluoromethyl-amino]-6-pyridin-4-yl-3H-pyrimidin-4-one  
 6-pyridin-4-yl-[(pyrid-2-ylmehtyl)-amino]-3H- pyrimidin-4-one,  
 6-pyridin-4-yl-[(pyrid-3-ylmehtyl)-amino]-3H- pyrimidin-4-one,  
 6-pyridin-4-yl-[(pyrid-4-ylmehtyl)-amino]-3H- pyrimidin-4-one,  
 2-[methyl-(2-pyridin-2-yl-ehtyl)-amino]-6-pyridin-4-yl-3H-pyrimidin-4-one,  
 20 or a salt thereof, or a solvate thereof or a hydrate thereof.

5. A medicament comprising as an active ingredient a substance selected from the group consisting of a pyrimidone derivative according to claim 1.

- 25 6. A GSK3 $\beta$  inhibitor selected from the group of a pyrimidone derivative according to claim 1.

7. Use of a compound according to claim 1 for the preparation of a medicament for preventive and/or therapeutic treatment of a disease caused by abnormal GSK3 $\beta$   
 30 activity.

8. Use of a compound according to claims 1 to 4 for the preparation of a medicament for preventive and/or therapeutic treatment of a neurodegenerative disease.

- 35 9. Use of a compound according to claim 8, wherein the disease is selected from the group consisting of Alzheimer's disease, Parkinson's disease, tauopathies, vascular dementia; acute stroke, traumatic injuries; cerebrovascular

accidents, brain cord trauma, spinal cord trauma; peripheral neuropathies; retinopathies or glaucoma.

10. Use of a compound according to claims 1 to 4 for the preparation of a  
5 medicament for preventive and/or therapeutic treatment of non-insulin dependent diabetes; obesity; manic depressive illness; schizophrenia; alopecia; or cancers.

11. Use according to claim 10 wherein cancer is breast cancer, non-small  
10 cell lung carcinoma, thyroid cancer, T or B-cell leukemia or virus-induced tumors

# INTERNATIONAL SEARCH REPORT

|   |   |  |
|---|---|--|
| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>IPC 7 C07D401/04 C07D401/14 A61K31/506 A61P25/28 C07D405/14<br>C07D409/14   |   | International Application No<br>PCT/EP 01/03638                  |
| According to International Patent Classification (IPC) or to both national classification and IPC   |   |  |
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>IPC 7 C07D A61K A61P  |   |  |
| Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched   |   |  |
| Electronic data base consulted during the international search (name of data base and, where practical, search terms used)<br>CHEM ABS Data   |   |  |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>   |   |  |
| Category *  | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No.  |
| A   | WO 98 24782 A (AMGEN)<br>11 June 1998 (1998-06-11)<br>cited in the application<br>page 0; claims  | 1-3,5  |
| A   | CHEMICAL ABSTRACTS, vol. 83, no. 1,<br>1975<br>Columbus, Ohio, US;<br>abstract no. 10129b,<br>page 854; column 1;<br>XP002145637<br>abstract<br>& JP 07 435634 A (MORI, H.)<br>25 September 1974 (1974-09-25) | 1-3,5  |
| -/--  |   |  |
| <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.   |   |  |
| * Special categories of cited documents :<br>*A* document defining the general state of the art which is not considered to be of particular relevance<br>*E* earlier document but published on or after the international filing date<br>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)<br>*O* document referring to an oral disclosure, use, exhibition or other means<br>*P* document published prior to the international filing date but later than the priority date claimed<br>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention<br>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone<br>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.<br>*8* document member of the same patent family |   |  |
| Date of the actual completion of the international search<br>5 July 2001  |   | Date of mailing of the international search report<br>13/07/2001 |
| Name and mailing address of the ISA<br>European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040. Tx. 31 651 epo nl,<br>Fax: (+31-70) 340-3016  |   | Authorized officer<br>Francois, J                                |

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 01/03638

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| A          | CHEMICAL ABSTRACTS, vol. 83, no. 28,<br>1975<br>Columbus, Ohio, US;<br>abstract no. 10127z,<br>page 853; column 2;<br>XP002127062<br>abstract<br>& JP 07 435633 A (MORI, H.)<br>25 September 1974 (1974-09-25)<br>----- | 1-3,5                 |



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 01/03638

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---------------------|----------------------------|---------------------|
| W0 9824782 A                              | 11-06-1998          | AU 5525498 A               | 29-06-1998          |
|   |                     | AU 733877 B                | 31-05-2001          |
|   |                     | AU 6012098 A               | 29-06-1998          |
|   |                     | BG 103512 A                | 31-07-2000          |
|   |                     | BG 103521 A                | 31-07-2000          |
|   |                     | BR 9713850 A               | 29-02-2000          |
|   |                     | BR 9713863 A               | 14-03-2000          |
|   |                     | CN 1246857 A               | 08-03-2000          |
|   |                     | CN 1246858 A               | 08-03-2000          |
|   |                     | CZ 9902015 A               | 17-11-1999          |
|   |                     | CZ 9902016 A               | 17-11-1999          |
|   |                     | EP 0948496 A               | 13-10-1999          |
|   |                     | EP 0948497 A               | 13-10-1999          |
|   |                     | HU 0001140 A               | 28-04-2001          |
|   |                     | HU 0001698 A               | 28-04-2001          |
|   |                     | WO 9824780 A               | 11-06-1998          |
|   |                     | US 6096753 A               | 01-08-2000          |
| JP 7435634 A                              |                     | NONE                       |                     |
| JP 7435633 A                              |                     | NONE                       |                     |

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau

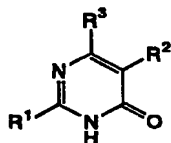


INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

|  |  |   |  |
|--|--|---|--|
| (51) International Patent Classification <sup>7</sup> :<br><b>C07D 401/04, 409/14, 401/14, A61K 31/506</b>   |  | <b>A1</b>   | (11) International Publication Number: <b>WO 00/18758</b>    |
|  |  |   | (43) International Publication Date: 6 April 2000 (06.04.00) |
| (21) International Application Number: PCT/JP99/05224  |  | <p>Mitsubishi Chemical Corporation, Yokohama Research Center, 1000, Kamoshida-cho, Aoba-ku, Yokohama-shi, Kanagawa 227-8502 (JP).</p> <p>(74) Agents: IMAMURA, Masazumi et al.; KRF Building, 5th floor, 5-5, Kyobashi 1-chome, Chuo-ku, Tokyo 104-0031 (JP).</p> <p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> |  |
| (22) International Filing Date: 24 September 1999 (24.09.99)   |  |   |  |
| (30) Priority Data:  |  |   |  |
| 10/271277 25 September 1998 (25.09.98) JP  |  |   |  |
| 10/305266 27 October 1998 (27.10.98) JP  |  |   |  |
| (71) Applicant (for all designated States except US): MITSUBISHI CHEMICAL CORPORATION [JP/JP]; 5-2, Marunouchi 2-chome, Chiyoda-ku, Tokyo 100-0005 (JP).   |  |   |  |
| (72) Inventors; and  |  |   |  |
| (75) Inventors/Applicants (for US only): WATANABE, Kazutoshi [JP/JP]; Mitsubishi Chemical Corporation, Yokohama Research Center, 1000, Kamoshida-cho, Aoba-ku, Yokohama-shi, Kanagawa 227-8502 (JP). ANDO, Ryoichi [JP/JP]; Mitsubishi Chemical Corporation, Yokohama Research Center, 1000, Kamoshida-cho, Aoba-ku, Yokohama-shi, Kanagawa 227-8502 (JP). SAITO, Ken-ichi [JP/JP]; Mitsubishi Chemical Corporation, Yokohama Research Center, 1000, Kamoshida-cho, Aoba-ku, Yokohama-shi, Kanagawa 227-8502 (JP). KAWAMOTO, Rie [JP/JP]; Mitsubishi Chemical Corporation, Yokohama Research Center, 1000, Kamoshida-cho, Aoba-ku, Yokohama-shi, Kanagawa 227-8502 (JP). SHODA, Aya [JP/JP]; |  |   |  |

Published  
With international search report.

(54) Title: PYRIMIDONE DERIVATIVES



(I)

(57) Abstract

A pyrimidone derivative represented by formula (I) or a salts thereof: wherein R<sup>1</sup> represents an alkyl group, an alkenyl group, an alkynyl group, a cycloalkyl group, an aryl group and the like; R<sup>2</sup> represents a hydrogen atom, hydroxyl group, an alkyl group, an alkenyl group and the like, R<sup>3</sup> represents a pyridyl group, and a medicament comprising said derivative or a salt thereof as an active ingredient which is used for preventive and/or therapeutic treatment of a disease caused by tau protein kinase I hyperactivity such as Alzheimer disease.

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

|    |                          |    |  |    |  |    |                          |
|----|--------------------------|----|--|----|--|----|--------------------------|
| AL | Albania                  | ES | Spain                                    | LS | Lesotho                                      | SI | Slovenia                 |
| AM | Armenia                  | FI | Finland                                  | LT | Lithuania                                    | SK | Slovakia                 |
| AT | Austria                  | FR | France                                   | LU | Luxembourg                                   | SN | Senegal                  |
| AU | Australia                | GA | Gabon                                    | LV | Latvia                                       | SZ | Swaziland                |
| AZ | Azerbaijan               | GB | United Kingdom                           | MC | Monaco                                       | TD | Chad                     |
| BA | Bosnia and Herzegovina   | GE | Georgia                                  | MD | Republic of Moldova                          | TG | Togo                     |
| BB | Barbados                 | GH | Ghana                                    | MG | Madagascar                                   | TJ | Tajikistan               |
| BE | Belgium                  | GN | Guinea                                   | MK | The former Yugoslav<br>Republic of Macedonia | TM | Turkmenistan             |
| BF | Burkina Faso             | GR | Greece                                   | ML | Mali   | TR | Turkey                   |
| BG | Bulgaria                 | HU | Hungary                                  | MN | Mongolia                                     | TT | Trinidad and Tobago      |
| BJ | Benin                    | IE | Ireland                                  | MR | Mauritania                                   | UA | Ukraine                  |
| BR | Brazil                   | IL | Israel                                   | MW | Malawi                                       | UG | Uganda                   |
| BY | Belarus                  | IS | Iceland                                  | MX | Mexico                                       | US | United States of America |
| CA | Canada                   | IT | Italy                                    | NE | Niger  | UZ | Uzbekistan               |
| CF | Central African Republic | JP | Japan                                    | NL | Netherlands                                  | VN | Viet Nam                 |
| CG | Congo                    | KE | Kenya                                    | NO | Norway                                       | YU | Yugoslavia               |
| CH | Switzerland              | KG | Kyrgyzstan                               | NZ | New Zealand                                  | ZW | Zimbabwe                 |
| CI | Côte d'Ivoire            | KP | Democratic People's<br>Republic of Korea | PL | Poland                                       |    |                          |
| CM | Cameroon                 | KR | Republic of Korea                        | PT | Portugal                                     |    |                          |
| CN | China                    | KZ | Kazakhstan                               | RO | Romania                                      |    |                          |
| CU | Cuba                     | LC | Saint Lucia                              | RU | Russian Federation                           |    |                          |
| CZ | Czech Republic           | LI | Liechtenstein                            | SD | Sudan  |    |                          |
| DE | Germany                  | LK | Sri Lanka                                | SE | Sweden                                       |    |                          |
| DK | Denmark                  | LR | Liberia                                  | SG | Singapore                                    |    |                          |
| EE | Estonia                  |    |  |    |  |    |                          |